DEPARTMENT OF HEALTH & HUMAN SERVICES

Health Resources and Services Administration

Rockville, MD 20857

To efficiently correspond with the HRSA FOIA Office during the COVID-19 public health emergency, we request that you communicate with us by email at FOIA@hrsa.gov or by telephone at 301-443-2865.

If you do not have access to email or choose not to use it, you can continue to send correspondence to the FOIA Office mailing address provided in this letter. However, this correspondence may be significantly delayed due to the COVID-19 pandemic.

May 5, 2021

Sent via Email
Vera Wilde
Linienstrasse 127
Berlin, Germany 10115
vera@verawil.de

Dear Ms. Wilde:

This letter acknowledges receipt of your Freedom of Information Act (FOIA) request received by this office on April 30, 2021. Your request has been assigned case number 21F164. You requested a fee waiver and your fee waiver is granted.

In summary, you requested Early Limited Formula for Treating Lactation Concerns (ELF-TLC) clinical trial documents and data. Specifically, you requested the following:

1. Early Limited Formula for Treating Lactation Concerns (ELF-TLC) clinical trial Institutional Review Board protocol including informed consent form;
2. ELF-TLC clinical trial adverse event reporting documents and data;
3. ELF-TLC clinical trial data and documents relating to how many participants were attempted to be recruited versus how many entered and remained in the trial; and
4. ELF-TLC clinical trial data and documents pertaining to follow-up of study participants who experienced adverse events.

Please note that the records you seek are maintained outside of this office and our staff has not yet been able to complete a search to determine whether the HRSA possesses records that are responsive to your request. Accordingly, we may be unable to comply with the 20 working-day time limit in this case, as well as the 10 additional days provided by the statute.

The actual processing time will depend on the complexity of your request and whether it involves sensitive records, voluminous records, extensive search, and/or consultation with other U.S. Department of Health and Human Services (HHS) components or other agencies. We anticipate responding to your request by the close of business on Thursday, July 1, 2021.

If some or all of the records you are requesting were submitted to the government (such as a grant application), additional steps may be required. Executive Order 12600, 52 FR 23781, and HHS FOIA regulation at 45 CFR § 5.42(a) require predisclosure notification for records that were submitted to the government where we have substantial reason to believe that information in the records could reasonably be considered confidential commercial information and exempt under FOIA Exemption 4.[1] HHS FOIA regulations provides the submitter with 10 working-days from the date of the notice to object to disclosure of part or all of the information contained in the records.

Once the records are returned by the submitter, we will review and consider all objections to release we receive within the time limit. If we decide to release the records, we will send written notice to the submitter advising of the release of records and also providing the submitter with a specific date that we intend to disclose the records, which must be at least 5 working-days after the date of the notice. See 45 CFR § 5.42(a)(3).

The FOIA and HHS FOIA regulations allow agencies to recover part of the costs of processing FOIA requests. You have been classified in the following manner:

☐ **Category 1 - Commercial Use Requester**. Category 1 requesters are charged for search time, documents review, and duplication.

☒ **Category 2 – Media, Educational, and Scientific Requester**. Category 2 requesters are charged for duplication only after the first 100 pages.

☐ **Category 3 – Other Requester.** Category 3 requesters are charged for search time (after 2 hours) and duplication (after 100 pages).

The FOIA and HHS FOIA regulations are available at the following web addresses:

- FOIA regulations: http://www.justice.gov/oip/foia-resources
- HHS FOIA regulations: https://www.hhs.gov/foia/statutes-and-resources/index.html

It is your responsibility to notify our office of any changes in your contact information (i.e., mailing address, telephone numbers, and/or email address). Any returned correspondence due to "unknown address" is considered sufficient reason to close your request.

You may contact this office 20 working-days from the date of this letter to inquire the status of your request. When making an inquiry, please refer to your case number.

If you are not satisfied with any aspect of the processing and handling of this request, please contact HRSA's FOIA Public Liaison:

Mr. Brian A. May
HRSA FOIA Public Liaison
U.S. Department of Health and Human Services
Health Resources and Services Administration

[1] https://www.justice.gov/archive/oip/foia_guide09/exemption4.pdf

Freedom of Information Office
5600 Fishers Lane, 13N114
Rockville, MD 20857
Telephone: 301-443-2865
Email: FOIA@hrsa.gov

and/or:

Office of Government Information Services
National Archives and Administration
8601 Adelphi Road – OGIS
College Park, MD 20740-6001
Telephone: 202-741-5770
Toll-Free: 877-684-6448
Fax: 202-741-5769
Email: ogis@nara.gov

If you have any questions please do not hesitate to contact me at 301-443-2865 or at FOIA@HRSA.gov.

Sincerely,

Latrice Gilliard
Government Information Specialist

From: **May, Brian (HRSA)** BMay@hrsa.gov
Subject: RE: HRSA FOIA 21F164 - Update
Date: 30. August 2021 at 13:08
To: Vera Wilde vera@verawil.de

BM

No problem, you are welcome. Looks like there is a line break in that hyperlink after "b996", that's probably why it didn't work. Hope that you have a great week.

Sincerely,

Brian
Brian A. May
Freedom of Information Act (FOIA) Officer
Executive Secretariat
Health Resources and Services Administration
Phone: 301-443-1467
Email: bmay@hrsa.gov

-----Original Message-----
From: Vera Wilde <vera@verawil.de>
Sent: Saturday, August 28, 2021 5:01 AM
To: May, Brian (HRSA) <BMay@hrsa.gov>
Cc: HRSA FOIA <FOIA@hrsa.gov>; Gilliard, Latrice (HRSA) <LGilliard@hrsa.gov>
Subject: Re: HRSA FOIA 21F164 - Update

Hi Mr. May,

Thank you for working on my request for ELF-TLC clinical trial documents and data, and for updating me on the status of the request.

It appears the link you sent is dead (“Not Found”), but I think I get the gist of the regulation from Cornell’s Legal Information Institute website.

I’ll look forward to your response, and again appreciate your working on and communicating about this request.

Have a great weekend.

Thanks and best,
Vera

> On 27. Aug 2021, at 21:02, May, Brian (HRSA) <BMay@hrsa.gov> wrote:
>
> Good Afternoon Vera:
>
> Hope that this email finds you well. Brief virtual introduction, I'm HRSA's "realively new" FOIA Officer, arrived here in late-March.
>
> Thanks for contacting us and requesting a status update. On Tuesday, August 24, 2021, we sent a Predisclosure Notice (see HHS FOIA regulation Subpart D) to the University of California, San Francisco on Tuesday, August 24, 2021 and requested a response by the close of business on September 7, 2021.
>
> Hyperlink to HHS FOIA reg:
> https://www.ecfr.gov/cgi-bin/retrieveECFRgp=&SID=f94e18d972b2eb4d4b996
> 0c0c23086b2&mc=true&n=pt45.1.5&r=PART&ty=HTML#sp45.1.5.d
>
> I'm anticipating that we will respond to your request by Friday, September 24, 2021. We will keep you updated on status of your request; in the interim, feel free to call me if you would like to discuss your request with me.
>
> Hope that you have a great weekend.
>
> Sincerely,
>
> Brian
> Brian A. May
> Freedom of Information Act (FOIA) Officer Executive Secretariat Health
> Resources and Services Administration
> Phone: 301-443-1467
> Email: bmay@hrsa.gov
>
> -----Original Message-----

From: Gilliard, Latrice (HRSA) <LGilliard@hrsa.gov>
Sent: Friday, August 27, 2021 1:20 PM
To: May, Brian (HRSA) <BMay@hrsa.gov>
Subject: FW: FOIA request - Early Limited Formula for Treating
Lactation Concerns (ELF-TLC) clinical trial documents and data

Hi Brian,

I understand this case was recently assigned to you. Ms. Wilde is asking for a status on this request. Please see below.

Thank you,

Latrice

-----Original Message-----
From: Vera Wilde <vera@verawil.de>
Sent: Friday, August 27, 2021 2:19 AM
To: Gilliard, Latrice (HRSA) <LGilliard@hrsa.gov>
Subject: Re: FOIA request - Early Limited Formula for Treating
Lactation Concerns (ELF-TLC) clinical trial documents and data

Dear Ms. Gilliard,

Thank you for working on my request for ELF-TLC clinical trial documents and data.

What is the status of the request? Can you please let me know when I can expect to receive the records?

Thanks and best regards,
Vera

> On 8. Jul 2021, at 20:30, Gilliard, Latrice (HRSA) <LGilliard@hrsa.gov> wrote:
>
> Hello Ms. Wilde,
>
> Unfortunately, my original anticipation was a little off. I believed I mentioned that I had several requests ahead of yours. Good news is that I am surely moving up in my queue.
>
> I can make note to check in with you once I have reviewed your request and the program's response. You are always welcome to check in with me as well. Thank you for your patience.
>
> Latrice
>
> -----Original Message-----
> From: Vera Wilde <vera@verawil.de>
> Sent: Thursday, July 8, 2021 4:41 AM
> To: Gilliard, Latrice (HRSA) <LGilliard@hrsa.gov>
> Subject: Re: FOIA request - Early Limited Formula for Treating
> Lactation Concerns (ELF-TLC) clinical trial documents and data
>
> Dear Ms. Gilliard,
>
> Just checking in again about my April 30 FOIA request. Your June 2 email had mentioned you anticipated responding by last week.
>
> Would it be possible / useful to have a quick phone call today to touch base?
>
> Thanks and best regards,
> Vera
>
>> On 3. Jun 2021, at 19:41, Vera Wilde <vera@verawil.de> wrote:
>>
>> Dear Ms. Gilliard,
>>
>> Thank you for your email. I appreciate receiving the acknowledgement letter, status update, and estimated response date.
>>
>> If you think it might be useful, I'd be happy to have a phone conversation or email exchange about the program office response when you've had a chance to review it. Maybe we can save everyone some time on formal back-and-forth communicating this way, if you think it appropriate to have some interim discussion.
>>
>> Thanks and best regards,
>> Vera

On 2. Jun 2021, at 19:49, Gilliard, Latrice (HRSA) <LGilliard@hrsa.gov> wrote:

Good Afternoon Ms. Wilde,

Thank you for your email. I apologized that you did not receive the attached acknowledgment letter previously. I was just assigned to work on your request. I will like to provide you with the most recent update to the status of your request- our office recently received a response from the program office. I have not had a chance to review that response. Currently, I have nine requests ahead of yours with an anticipated date of response to your request by Thursday, July 1, 2021.

Please take a moment to review the attached acknowledgment letter and please let me know if you have any additional questions. Feel free to email me for any status.

Thank you for your patience,

Latrice

-----Original Message-----
From: HRSA FOIA <FOIA@hrsa.gov>
Sent: Tuesday, June 1, 2021 7:34 AM
To: Gilliard, Latrice (HRSA) <LGilliard@hrsa.gov>
Subject: FW: FOIA request - Early Limited Formula for Treating
Lactation Concerns (ELF-TLC) clinical trial documents and data

FYI

-----Original Message-----
From: Vera Wilde <vera@verawil.de>
Sent: Tuesday, June 1, 2021 12:38 AM
To: HRSA FOIA <FOIA@hrsa.gov>
Subject: Re: FOIA request - Early Limited Formula for Treating
Lactation Concerns (ELF-TLC) clinical trial documents and data

Dear Ms. Coutain,

Just checking in again about this FOIA request I submitted over four weeks ago now. I never heard back, and am wondering why.

At your convenience, would you please let me know the status of the request? I would like to confirm it is in process and obtain an estimated completion date if possible.

Thanks and best regards,
Vera

> On 17. May 2021, at 14:44, Vera Wilde <vera@verawil.de> wrote:
>
> Dear Ms. Coutain,
>
> I just left you a voice message, and wanted to also send a quick email to check on the status of this FOIA request I submitted two weeks ago.
>
> I have not received any acknowledgment so far. Would it be possible to please give me an estimated completion date? And please let me know if anything else is needed.
>
> Thanks and best regards,
> Vera
>
> > On 30. Apr 2021, at 23:56, Vera Wilde <vera@verawil.de> wrote:
> >
> > April 30, 2021
> >
> > Health Resources and Services Administration (HRSA) Angeletta
> > Coutain, Acting Freedom of Information Officer
> > 5600 Fishers Lane, Room 13-N82
> > Rockville, Maryland 20857
> > Phone: 301-443-2865
> >
> > Re: FOIA Request - Early Limited Formula for Treating Lactation
> > Concerns (ELF-TLC) clinical trial documents and data
> >
> > Dear Ms. Coutain:
> >
> > Under the Freedom of Information Act (5 U.S.C. Section 552), I am requesting the following documents and data:

Under the Freedom of Information Act (5 U.S.C. Section 552), I am requesting the following documents and data:

1. Early Limited Formula for Treating Lactation Concerns (ELF-TLC) clinical trial Institutional Review Board protocol including informed consent form; 2. ELF-TLC clinical trial adverse event reporting documents and data; 3. ELF-TLC clinical trial data and documents relating to how many participants were attempted to be recruited versus how many entered and remained in the trial; and 4. ELF-TLC clinical trial data and documents pertaining to follow-up of study participants who experienced adverse events.

In relation to each item, please include any attachments or supporting documents.

As a representative of the news media (a freelance writer previously published with outlets including *The Guardian* and *Christian Science Monitor* - see https://verawil.de/publications/) and new mom researching a book on breastfeeding, I am gathering information on preventable harms to newborns from exclusive breastfeeding promotion. This information is of current interest to the public because published medical studies dating back in some cases decades indicate rising incidences of preventable newborn rehospitalizations due to dehydration and starvation when breastfeeding does not work well enough and formula supplementation is not offered. These rising rates of phenomena like jaundice and hypernatremia can cause permanent brain damage and even death in previously healthy newborns. There have been numerous recent mainstream news stories on the work of the Fed Is Best Foundation, a U.S. non-profit organisation started in 2016 to raise awareness, educate, and help prevent these harms. But in spite of sufficient medical evidence according to experts, and vocal advocacy efforts including from moms of affected babies, exclusive breastfeeding promotion policies and practices continue to be widespread and in some cases still growing.

That is the context in which the ELF-TLC clinical trial first identified high-risk, exclusively breastfed infants from substantial early weight loss, and then limited early formula supplementation to 10 mL per feeding in the treatment group. The control group was not supplemented. One treatment-group infant and three controls were subsequently readmitted for hyperbilirubinemia, a potentially life and brain-threatening complication of untreated jaundice that can result from neonatal starvation. (See, e.g., multiple meta-analyses associating neonatal jaundice with later development of autism - https://pubmed.ncbi.nlm.nih.gov/?term=neonatal+jaundice+autism .) There was no evidence (known to me) before this trial that 10 mL was sufficient in this context, and discussion with associated researchers did not indicate any such evidence. There was no evidence that not supplementing the control-group babies was safe. This leaves me wondering how this research was conceptualised in terms of risks and benefits. How was the IRB informed of relevant risks and asked to weigh them against benefits? How were parents informed? Was either party really fully informed, or was this research potentially conducted without legitimate informed consent or full IRB oversight given its actual risks of preventable harm to newborns?

Please take note of the Office of Management and Budget guidelines published March 27, 1987 (52 FR 10012) that include electronic publications and other nontraditional publishers as representatives of the news media. OMB guidelines say that past publication can be used as proof I am a media representative. Please also remember that the U.S. Court of Appeals for the District of Columbia has determined that even a nonprofit clearinghouse of information can qualify as a representative of the news media. See National Security Archive v. U.S. Department of Defense, 279 U.S. App. D.C. 308 (D.C. 1989). This is relevant because I plan to make the information obtained via this request freely available online no matter where any resultant publications may run. I have an established record of doing this with substantive responses to other FOIA requests, having worked with multiple online outlets (including Russ Kick's AltGov2 and The Memory Hole) and in collaboration with multiple widely circulated print publications (including McClatchy News - syndicated nation-wide, and Wired) to do so. There are several links proving these collaborations on my website: https://verawil.de/polygraph/ .

Please note that 5 U.S.C. Section 552(a)(4)(A)(iv)(II) requires that you provide the first 100 copies to me at no charge.

However, I am requesting a waiver of all fees under 5 U.S.C. Section 552(a)(4)(A)(iii). The information I seek is in the public interest because it will contribute significantly to public understanding of the operations or activities of the government and is not primarily in my commercial interest. The government activity at issue here is this trial, in which HRSA/Maternal and Child Health Bureau is listed as a Collaborator.

I believe I meet the criteria for a fee waiver recognized by the U.S. Justice Department - in its policy guidance of April 1987 - and by the federal courts, See Project on Military Procurement v. Department of the Navy, 710 F. Supp. 362 363, 365 (D.C.D. 1989).

Also, the information sought has informative value, or potential for contribution to public understanding. Please note the decision in Elizabeth Eudey v. Central Intelligence Agency, 478 F. Supp. 1175 1176 (D.C.D. 1979) (even a single document has the potential for contributing to public understanding). I plan to disseminate this information to the public at large in the following manner: First, I will learn from the information in my larger research project. Then, I will try to place resultant work as a writer. Next, if that is not working, I will try placing stories as a source. I am always on the lookout for journalists already doing good work from good platforms with whom to collaborate (as I have demonstrably done in the past, e.g., with McClatchy and Wired journalists) in order to more broadly disseminate information when the opportunity presents. Finally, if I wind up in a position where the information has supported my research but still not been published and I feel its currency is aging, I will just post it on my website and keep working on broader dissemination through writing and journalistic collaboration efforts alike. In that case, I would also consider sharing it with the Fed Is Best Foundation to potentially post on their website, since they would get more traffic and the idea is always just to get the information out as broadly and well as possible.

In addition, the release of this information will have a significant impact on public understanding because I think there is a lack of knowledge on the part of the public about how frequently exclusive breastfeeding does not work

and how seriously this can harm babies. If parents in this study were not adequately informed about the risks, it would highlight how doctor-patient trust can be abused in this context. If, on the other and, the parents actually were adequately informed and still chose to accept risks of 100% preventable harms to their babies who sometimes went on to be rehospitalized, it would highlight how the current consensus on "Breast is Best" can even cause parents to choose avoidable risk of serious harm for their newborn babies over just offering them a bottle to protect their brains and stay out of the hospital. The collaboration of HRSA in either scenario would show the public how the government has participated in recent breastfeeding medicine research. If something else I have not imagined is really what happened here, then hopefully the requested documents and data will also correct my understanding.

In your deliberations, please take note of the following cases: Campbell v. U.S. Department of Justice, 334 U.S. App. D.C. (1998)(administrative and seemingly repetitious information is not exempt from fee-waiver consideration); Project on Military Procurement (agencies cannot reject a fee waiver based on the assumption that the information sought is covered by a FOIA exemption; and Landmark Legal Foundation v. Internal Revenue Service, 1998 U.S. Dist. LEXIS 21722 (D.C.D. 1998) (the fact that the information will soon be turned over to a public body does not exempt the material from fee-waiver consideration).

I look forward to your response within the 20 working days, as outlined by the statute.

Thank you for your time, consideration, and assistance.

Best regards,
Vera Wilde

Linienstrasse 127
Berlin, Germany 10115
+49 151 5907 5245
vera@verawil.de

<5.5.21 21F164 Wilde Acknowledgment Letter.pdf>

DEPARTMENT OF HEALTH & HUMAN SERVICES

Health Resources and Services Administration

Rockville, MD 20857

To efficiently correspond with the HRSA FOIA Office during the COVID-19 public health emergency, we request that you communicate with us by email at FOIA@hrsa.gov or by telephone at 301-443-2865.

If you do not have access to email or choose not to use it, you can continue to send correspondence to the FOIA Office mailing address provided in this letter. However, this correspondence may be significantly delayed due to the COVID-19 pandemic.

September 8, 2021

Sent via Email
Vera Wilde
Linienstrasse 127
Berlin, Germany 10115
vera@verawil.de

Re: Health Resources and Services Administration (HRSA) Freedom of Information Act (FOIA) Request Case Number 21F164

Dear Vera Wilde:

This is the final response to your FOIA request dated April 30, 2021. In summary, you requested Early Limited Formula for Treating Lactation Concerns (ELF-TLC) clinical trial documents and data. Specifically, you requested the following records:

1. Early Limited Formula for Treating Lactation Concerns (ELF-TLC) clinical trial Institutional Review Board protocol including informed consent form;
2. ELF-TLC clinical trial adverse event reporting documents and data;
3. ELF-TLC clinical trial data and documents relating to how many participants were attempted to be recruited versus how many entered and remained in the trial; and
4. ELF-TLC clinical trial data and documents pertaining to follow-up of study participants who experienced adverse events.

A records search was conducted in HRSA's Maternal and Child Health Bureau (MCHB) and we located 67 pages of responsive records. When requesting a grant application or contract, Executive Order (E.O.) 12600[1] and U.S. Department of Health and Human Services (HHS)

[1] https://www.archives.gov/federal-register/codification/executive-order/12600.html

FOIA regulations at 45 C.F.R. § 5.42(a)[2] require federal agencies to notify submitters of confidential commercial information that there has been a FOIA request for their information. We coordinated a Predisclosure Notice with the submitter who objected to the release of portions of the records. Therefore, we reasonably foresee that disclosure would harm an interest protected by one or more of the nine exemptions to the FOIA's general rule of disclosure. We withheld portions of two pages under FOIA exemption, 5 U.S.C. § 552(b)(4)(Exemption 4).

Exemption 4 protects "trade secrets and commercial or financial information obtained from a person [that is] privileged or confidential." The withheld information is "commercial or financial information". The entity that supplied this information (the submitter) is considered a person, because the term "person," under the FOIA, includes a wide range of entities including "universities". Finally, the submitter does not customarily release this information to the public and HRSA provided the submitter an assurance of confidentiality; therefore, the information is confidential for the purposes of Exemption 4. We withheld the future study designs listed on two pages.

MCHB provided additional background information in response to your request. Regarding item 1, MCHB did not receive an informed consent form from the submitter; therefore we do not possess any responsive records. In response to item 2, the trial did not report adverse events. In the protocol, the grantee did not expect any adverse events. There might be the potential concern of a loss of privacy for the study participants and the grantee identified activities to protect against the risk in the protocol. Regarding item 3, 4,739 newborns were assessed for eligibility (4,168 did not meet the inclusion criteria). Of those, 164 newborns were recruited; 82 were in the ELT group and 82 were in the exclusive breastfeeding group. 152 newborns remained in the trial; eight lost follow up in the ELT group and four lost follow up in the exclusive breastfeeding group (see Figure 1s in the publications). Finally, we do not possess any data in response to item 4.

HHS policy calls for the fullest responsible disclosure consistent with the requirements of administrative necessity and confidentiality as recognized by the FOIA, 5 U.S.C. § 552 and HHS' FOIA regulations at 45 CFR Part 5.

If you believe that the information withheld should not be exempt from disclosure or that this response constitutes an adverse determination, you may appeal. By filing an appeal, you preserve your rights under FOIA and give the agency a chance to review and reconsider your request and the agency's decision.

Your appeal can be submitted by email or in the HHS FOIA and Appeal Portal within 90 days from the date of this letter to:

Carol Maloney
Deputy Agency Chief FOIA Officer
U.S. Department of Health and Human Services
Office of the Assistant Secretary for Public Affairs

[2] https://www.ecfr.gov/cgi-bin/retrieveECFR?gp=&SID=f94e18d972b2eb4d4b9960c0c23086b2&mc=true&n=pt45.1.5&r=PART&ty=HTML#se45.1.5_142

Email: FOIARequest@hhs.gov
Portal: https://requests.publiclink.hhs.gov/App/Index.aspx

If you would like to discuss our response before filing an appeal to attempt to resolve your dispute without going through the appeals process, you may contact me as HRSA's FOIA Public Liaison for assistance:

Brian A. May
HRSA FOIA Public Liaison
U.S. Department of Health and Human Services
Health Resources and Services Administration
Freedom of Information Act Office
5600 Fishers Lane, 13N114
Rockville, MD 20857
Telephone: 301-443-2865
Email: FOIA@hrsa.gov

If we are unable to resolve your FOIA dispute, the Office of Government Information Services (OGIS), the federal FOIA Ombudsman's office, offers mediation services to help resolve disputes between FOIA requesters and federal agencies. The contact information for OGIS is:

Office of Government Information Services
National Archives and Records Administration
8601 Adelphi Road–OGIS
College Park, MD 20740-6001
Telephone: 202-741-5770
Toll-Free: 1-877-684-6448
Fax: 202-741-5769
Email: ogis@nara.gov

On May 5, 2021, we granted your request for a fee waiver.

If you have any questions, please do not hesitate to contact my office at 301-443-2865 or FOIA@hrsa.gov.

Sincerely,

Brian A. May
Freedom of Information Act Officer

Enclosure
21F164_Combined_Records
_Redacted.pdf (67 pages)

JAMA PEDIATRICS

JAMA Pediatr. 2019 Aug; 173(8): 729–735.
Published online 2019 Jun 3. doi: 10.1001/jamapediatrics.2019.1424

PMCID: PMC6547125
PMID: 31157878

Effect of Early Limited Formula on Breastfeeding Duration in the First Year of Life

A Randomized Clinical Trial

Valerie J. Flaherman, MD, MPH[1,2] Michael D. Cabana, MD, MPH,[1,2] Charles E. McCulloch, PhD,[2] and Ian M. Paul, MD, MSc[3]
Author information Article notes Copyright and License information Disclaimer

This article has been corrected. See JAMA Pediatr. 2019 August 01; 173(8): 801.

Associated Data

Supplementary Materials

Go to:

Key Points

Question

Does structured, short-term formula supplementation for at-risk term neonates affect the proportion still breastfeeding at 6 and 12 months?

Findings

In this randomized clinical trial that enrolled 164 mother-newborn dyads with newborn weight loss at or above the 75th percentile for hour of age, structured, short-term neonatal formula supplementation did not affect breastfeeding prevalence at 6 months.

Meaning

Using neonatal formula supplementation in a structured, short-term manner did not affect breastfeeding through 6 months; further research is needed to determine its effect on breastfeeding through the recommended duration of 12 months.

Go to:

Abstract

Importance

Breastfeeding through 6 and 12 months are 2 goals of the Centers for Disease Control and Prevention Healthy People 2020 initiative, but the 6-month goal is met for only 52% of US infants and the 12-month goal for 30% of US infants.

Objective

To determine whether structured, short-term formula supplementation for at-risk neonates affects the proportion still breastfeeding at 6 and 12 months.

Design, Setting, and Participants

This randomized clinical trial conducted at 2 US academic medical centers enrolled 164 exclusively breastfeeding mother-infant dyads of mothers who were not yet producing copious milk and infants who were 24 to 72 hours old with newborn weight loss at or above the 75th percentile for age. Participants were enrolled from January 2015 through September 2016.

Interventions

Early Limited Formula (ELF), a structured formula supplementation protocol (10 mL formula fed after each breastfeeding until mothers produced copious milk), compared with control dyads, who continued exclusive breastfeeding and received a safety teaching intervention.

Main Outcomes and Measures

The study's primary outcome was any breastfeeding at 6 months. Secondary outcomes included age at breastfeeding cessation and any breastfeeding at 12 months. All outcomes were assessed by maternal phone survey.

Results

Eighty-two newborns were randomized to ELF and 82 to the control group. Mean (SD) maternal age was 31.4 (5.9) years, and 114 (69.5%) self-identified as non-Hispanic white; 20 (12.2%), Hispanic; 17 (10.4%), Asian; 5 (3.0%), non-Hispanic black; and 7 (4.3%), other. Compared with controls, mothers randomized to ELF were less likely to be married (n = 53 [64.6%] vs n = 66 [80.5%]; *P* = .03) and had shorter mean (SD) intended duration of breastfeeding (8.6 [3.4] vs 9.9 [4.4] months; *P* = .049). Median (interquartile range) duration of breastfeeding in the cohort was 9 (6-12) months. At 6 months, 47 (65%) infants randomized to ELF were breastfeeding, compared with 60 (77%) of the control infants (absolute difference, –12%; 95% CI, –26% to 3%; *P* = .12). At 12 months, 21 of the 71 ELF infants available for analysis (29.6%) were breastfeeding, compared with 37 of the available 77 (48.1%) control infants (risk difference, –18%; 95% CI, –34% to –3%). Marital status and intended breastfeeding duration were both associated with breastfeeding duration; models adjusting for these found a hazard ratio for time-to-event of breastfeeding cessation through 12 months of 0.74 (95% CI, 0.48-1.14) for ELF infants compared with infants in the control group.

Conclusions and Relevance

In this cohort with high breastfeeding prevalence, ELF was not associated with any improvement in breastfeeding duration. Future research should examine the effect of ELF in populations at higher risk of early cessation.

Trial Registration

ClinicalTrials.gov identifier: NCT02313181

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Introduction

Numerous epidemiologic and observational[1,2,3,4] studies have found that duration of breastfeeding is shorter for infants who receive formula in the early newborn period.[5,6,7,8] This observed association has informed clinical guidelines and public health initiatives that discourage the use of formula during the birth hospitalization.[9,10,11,12] However, the causal relationship between early formula and reduced breastfeeding duration is uncertain, because 3 randomized clinical trials have not demonstrated a deleterious effect of early supplementation on breastfeeding duration.[13,14,15] Because formula may ameliorate neonatal hyperbilirubemia and dehydration, exclusively breastfed infants may be at increased risk of early morbidity from these sources.

A structured, short-term formula supplementation protocol called Early Limited Formula (ELF), which delivers 10 mL of formula by syringe after each breastfeeding until the onset of copious maternal milk, improved the prevalence of breastfeeding and of exclusive breastfeeding at 3 months for newborns enrolled in a small pilot randomized trial conducted from 2009 through 2011.[15] To examine whether ELF might improve breastfeeding duration through 6 and 12 months in a larger cohort, we conducted the study of Early Limited Formula for Treating Lactation Concerns (ELF-TLC). Initial ELF-TLC findings revealed no effect of ELF on breastfeeding or intestinal microbiota through 1 month of age; a trend toward reduced readmission was also noted.[16] Below, we report the effect of ELF in ELF-TLC on breastfeeding at 6 and 12 months of age.

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Methods

Trial Design, Participants, and Setting

This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline. Early Limited Formula for Treating Lactation Concerns enrolled 164 healthy, exclusively breastfeeding term (≥37 weeks) singletons born at the University of California, San Francisco Medical Center (San Francisco) and at Penn State Milton S. Hershey Medical Center (Hershey, Pennsylvania) between January 2015 and September 2016 (Figure 1). Infants were included if they were 24 to 48 hours old and had weight loss at or above the 75th percentile on the Newborn Weight Tool (http://www.newbornweight.org) and mothers who had not yet begun copious milk production.[17] Weight measurement to determine eligibility for enrollment was obtained during routine hospital care. Infants were excluded if birth weight was less than 2500 g, the clinical team had recommended against breastfeeding, they had received formula, required a greater level of care than a level 1 nursery, had mothers who were aged younger than 18 years or could not speak English, were not expected to be discharged home with their parents, or were being observed for narcotic abstinence syndrome. Infants were also excluded if they had already lost 10% or more of their birth weight, because such infants commonly received supplementation in both enrolling hospitals. Before recruiting the first participant, ELF-TLC was approved by the University of California San Francisco Committee on Human Research and the Human Subjects Protection Office at Penn State College of Medicine. A study nurse obtained informed consent from mothers for both mother and infant prior to enrollment (Trial Protocol in Supplement 1).

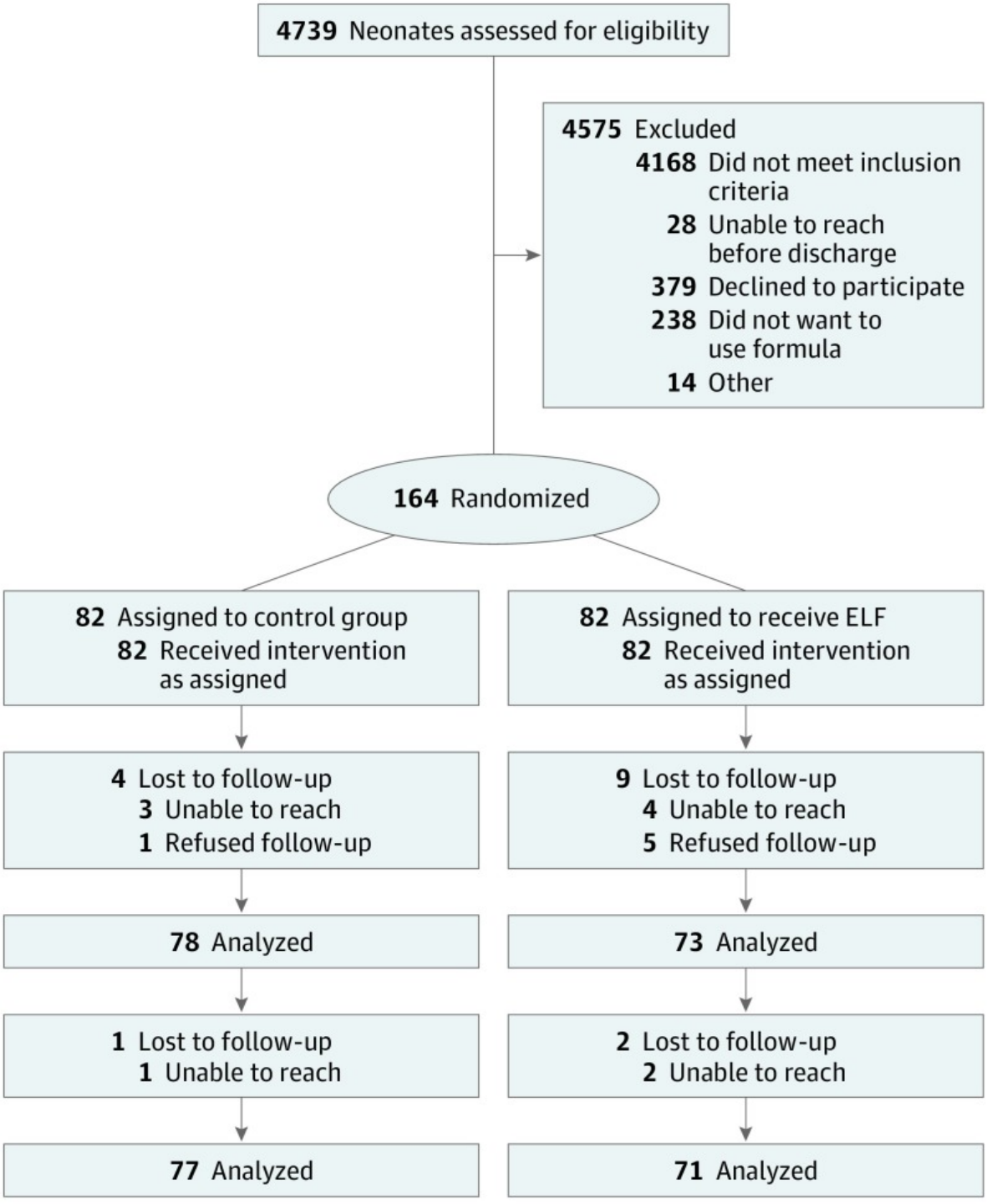

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Figure 1.

CONSORT diagram for the Early Limited Formula for Treating Lactation Concerns (ELF-TLC) Randomized Clinical Trial

Recruitment and Randomization

A randomized allocation sequence was generated by an independent biostatistician using a password-encoded Excel spreadsheet with randomly permuted blocks of 2 and 4 participants stratified on location (University of California, San Francisco or Pennsylvania State University) and on method of delivery (vaginal or cesarean). After obtaining informed consent, the study nurse accessed this randomized allocation sequence to determine treatment assignment. Newborns enrolled in ELF-TLC were randomly assigned in a 1:1 ratio either to breastfeeding with ELF (intervention) or to continue exclusive breastfeeding with a safety intervention (control). Recruitment was stopped when target enrollment was achieved.

Interventions

For dyads randomly assigned to the ELF intervention group, study nurses supported mothers in breastfeeding their infant and then taught mothers to use a feeding syringe to deliver 10 mL of formula to their infants immediately after each time they breastfed before the onset of copious breast milk. This ELF intervention was taught using extensively hydrolyzed formula (Nutramigen; Mead Johnson, Inc), both because of the potential benefits of extensively hydrolyzed formula[18] and because of its successful use in previous work.[15] Mothers were instructed to discontinue using ELF once they had begun copious milk production.

For dyads randomly assigned to the control group, study nurses supported mothers in breastfeeding their infant and then instructed mothers to breastfeed exclusively unless directed by a health care practitioner. To control for the time and attention that study nurses gave to mothers of ELF infants while teaching the ELF technique, study nurses taught infant safety techniques (including household water temperature, car seat position, and safe infant sleep environment) to mothers in the control group for 15 minutes. Both groups received a single nurse visit.

For both groups, at the time of enrollment, the study nurse completed a survey querying mothers regarding demographic and clinical characteristics as well as previous breastfeeding experience and intention. After the study nurse completed this initial assessment and teaching, no additional clinical management was provided by ELF-TLC, and enrolled infants resumed usual care with their clinicians. Before beginning enrollment and again at the midpoint of enrollment, the principal investigator (V.J.F.) trained all study nurses in breastfeeding support, use of ELF, and delivery of the safety control intervention.

Measures

All outcomes were assessed by phone survey of mothers. Our institutional review board–approved protocol's primary outcome, breastfeeding at 6 months, was assessed by a research assistant blinded to treatment allocation with the item, "Has your baby breastfed or received any breast milk in the past 24 hours?" This item was also used to assess breastfeeding duration through 12 months. At the first assessment at which a mother responded "no" to the item "Has your baby breastfed or received any breast milk in the past 24 hours?," age at breastfeeding cessation was assessed using the item, "How old was [name of child] when he/she completely stopped breastfeeding or being fed breast milk?" Exclusive breastfeeding was assessed using the following items: "How old was [name of child] when he/she was first fed formula?"; "How old was [name of child] when he/she was first fed anything other than breast milk or formula?"; "In the past 7 days, how often was your baby fed formula?"; and "In the past 7 days, how often was your baby fed something other than breast milk or formula?" Infants who were fed either formula or something other than breast milk or formula were defined as not exclusively breastfeeding. Intended breastfeeding duration was assessed at enrollment using the item, "For how long are you planning to breastfeed?"

Statistical Analysis

Estimating 10% dropout by the time of primary outcome assessment at 6 months, a sample size of 164 newborns was selected to achieve outcomes for 148 infants at 6 months and thereby achieve 90% power (α = .05) to detect a relative risk of 1.4 for ELF vs control with respect to the primary outcome of breastfeeding prevalence at 6 months of age, which was estimated at 60%.[5,8,19,20,21,22,23,24,25] χ^2 Testing was used to compare the ELF and control groups with respect to this primary outcome as well as with respect to other clinically meaningful dichotomous variables. The Fisher exact test was used to compare ELF and control data in prespecified subgroups of household income levels. Relative risks were calculated for the primary outcome and risk differences were calculated for both primary and secondary outcomes. Wald-based CIs (calculated on the log scale for relative risks) were also given. With respect to the secondary outcome of time-to-event of breastfeeding cessation, Cox proportional hazards analysis was used to compare the ELF and control groups and to compare clinically meaningful dichotomous predictor variables.

Our approach to multivariable analysis was as follows. For clinically meaningful variables that demonstrated an association with both treatment assignment and breastfeeding status and were therefore potential confounding variables, we assessed whether adjustment for the potential confounding variable attenuated the relationship between treatment assignment and breastfeeding and whether there was no interaction between treatment assignment and the potential confounding variable. For potential confounding variables that had no interaction with treatment assignment, we included the potential confounding variable in multivariable analysis of the effect of treatment assignment on breastfeeding without adding an interaction term. Multivariable logistic regression was used to compare dichotomous outcomes and multivariable Cox proportional hazards analysis was used to compare time-to-event outcomes between the ELF and control groups while adjusting for clinically meaningful potential confounding variables and stratification variables. For clinically meaningful dichotomous predictor variables that varied significantly between the ELF and control groups and for site of enrollment, we also analyzed the effect of ELF on breastfeeding prevalence at 6 and 12 months by subgroup using χ^2 testing.

All analyses of the effect of random assignment to ELF were by intention to treat and were conducted in Stata version 14.1 (Stata Corp). In addition to the above intention-to-treat analyses of the effect of ELF on outcomes, we also explored, independent of treatment assignment, the relationship between formula use at 1 week of age and breastfeeding practices using Wald CIs and Cox proportional hazards analysis. All tests for statistical significance were 2 sided and $P<.05$ indicated statistical significance.

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Results

Of 571 eligible mother-infant dyads, ELF-TLC enrolled 164 (28.7%); of 407 (71.3%) who were not enrolled, 238 (58.5%) stated they did not want to use formula. Enrolled infants had a mean (SD) gestational age of 39.4 (1.1) weeks and chronological age of 35.9 (9.2) hours (Table 1). Enrolled mothers had a mean (SD) age of 31.4 (5.9) years; 110 (67.1%) had completed college, 112 of 150 who responded to income questions (74.6%) reported a household income greater than $50 000, and 114 (69.5%) self-identified as non-Hispanic white. Compared with controls, mothers of infants randomly assigned to ELF were less likely to be married (53 of 80 [66.0%] vs 66 of 81 [81.5%]; *P* = .03) and had a mean (SD) intended duration of breastfeeding that was shorter (8.6 [3.4] vs 9.9 [4.4] months; *P* = .049). Median (interquartile range [IQR]) duration of ELF use after treatment assignment was 2 (1.5-3.0) days. At 12 months post-partum, 149 mothers (90.8%) responded to the final survey; attrition did not differ by treatment assignment.

Table 1.

Baseline Demographic and Clinical Characteristics by Treatment Assignment to Early Limited Formula or Continued Exclusive Breastfeeding

Characteristic	No. (%)	
	Early Limited Formula Group (Intervention) (n = 82)	Continued Exclusive Breastfeeding (Control) (n = 82)
Gestational age, mean (SD), wk	39.4 (1.2)	39.4 (1.1)
Vaginal delivery	61 (74.4)	60 (73.1)
Infant age at enrollment, mean (SD), h	35.7 (9.5)	36.1 (9.0)
Maternal age, mean (SD), y	31.3 (5.6)	31.6 (6.2)
Enrolled at Pennsylvania State University	40 (48.8)	40 (48.8)
Maternal race/ethnicity		
Non-Hispanic white	57 (69.5)	57 (69.5)
Non-Hispanic black	3 (3.6)	2 (2.4)
Hispanic	10 (12.2)	10 (12.2)

Characteristic	No. (%)	
	Early Limited Formula Group (Intervention) (n = 82)	Continued Exclusive Breastfeeding (Control) (n = 82)
Asian	9 (11.0)	8 (9.8)
Other	2 (2.4)	5 (6.1)
Maternal educational attainment		
8th grade or less	1 (1.2)	0 (0)
Some high school	2 (2.4)	2 (2.4)
High school graduate	4 (4.9)	9 (11.0)
Some college or technical school	21 (25.6)	12 (14.6)
Completed college	33 (40.2)	31 (37.8)
Postgraduate training	19 (23.2)	27 (32.9)
Married[a]	53 (66.0)	66 (81.5)

Characteristic	No. (%)	
	Early Limited Formula Group (Intervention) (n = 82)	Continued Exclusive Breastfeeding (Control) (n = 82)
Primiparous[b]	51 (63)	48 (58.5)
% Weight loss at enrollment, mean (SD)	6.3 (1.6)	6.4 (1.5)
Birth weight, mean (SD), g	3372 (670)	3398 (453)
US born	66 (80.5)	66 (82)
Mother with breastfeeding experience	32 (39.0)	31 (37.8)
Intended breastfeeding duration, mean (SD), mo	8.6 (3.4)	9.9 (4.4)
Household annual income, $		
<10 000	3 (3.7)	1 (1.2)
10 000-24 999	8 (9.8)	7 (8.5)
25 000-49 999	10 (12.2)	9 (11.0)

Characteristic	No. (%)	
	Early Limited Formula Group (Intervention) (n = 82)	Continued Exclusive Breastfeeding (Control) (n = 82)
50 000-74 999	12 (14.6)	4 (4.9)
75 000-100 000	4 (4.9)	11 (13.4)
>100 000	37 (45.1)	44 (53.7)
Unknown/declined	8 (9.8)	6 (7.3)

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[a]Calculated from denominator 80 for the Early Limited Formula group and 81 for control group.

[b]Calculated from denominator of 81 for the Early Limited Formula group.

Effect of Treatment Assignment on Breastfeeding Duration

The relative risk for ELF compared with control with respect to the outcome of breastfeeding prevalence at 6 months was 0.85 (95% CI, 0.69-1.04) (Table 2). Treatment assignment also did not affect the prevalence of exclusive breastfeeding at 6 months. Breastfeeding prevalence at 12 months was lower for those randomly assigned to ELF at birth. In bivariate Cox proportional hazards analysis, infants in the ELF group had a shorter time to breastfeeding cessation through 12 months than infants in the control group (hazard ratio [HR], 0.65 [95% CI, 0.43-0.97] months) (Figure 2). No beneficial or detrimental effect of ELF on breastfeeding at 6 months was demonstrated for any subgroup, including subgroups of household income, maternal marital status, maternal educational attainment, and site of enrollment; at 12 months, breastfeeding prevalence was lower for infants assigned to ELF in the subgroup of high-income mothers and the subgroup enrolled at the University of California, San Francisco (eTable 1 in Supplement 2).

Table 2.

Adjusted and Unadjusted Analysis of Interval Breastfeeding Prevalence by Treatment Assignment

Outcome(s)	No. (%)		Unadjusted (95% CI)		Adjusted (95% CI)[a]	
	Early Limited Formula	Control	Absolute Risk Difference	Hazard Ratio	Odds Ratio	Hazard Ratio
Primary						
Breastfeeding at 6 mo	47 (65)	60 (79)	−12% (−26 to 3)	NA	0.60 (0.24 to 1.38)	NA
Secondary						
Exclusive breastfeeding at 6 mo	25 (35)	36 (46)	−11% (−27 to 4)	NA	0.69 (0.33 to 1.44)	NA
Breastfeeding at 12 mo	21 (30)	37 (48)	−18% (−34 to −3)	NA	0.70 (0.30 to 1.59)	NA
Time-to-event of breastfeeding cessation	NA	NA	NA	0.65 (0.43 to 0.97)		0.74 (0.48 to 1.14)

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Abbreviation: NA, not applicable.

[a]Adjusted for site of enrollment, method of delivery and maternal marital status and intended duration of breastfeeding.

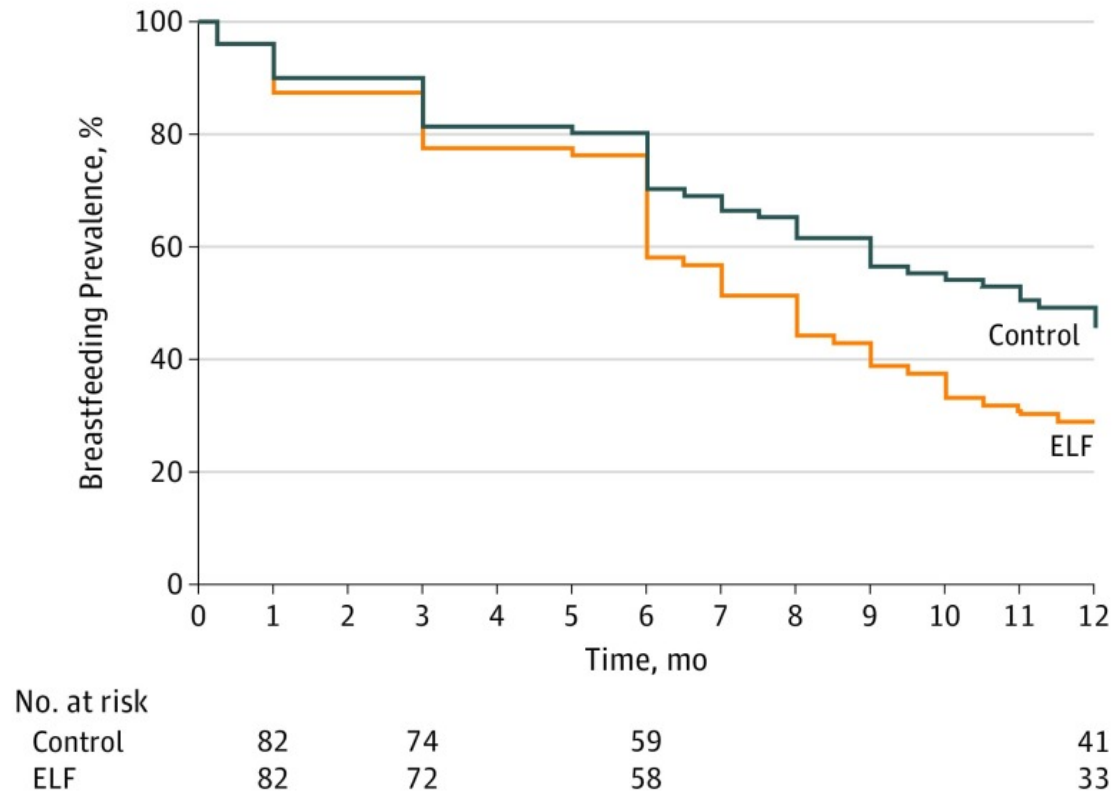

Figure 2.
Breastfeeding Cessation Through 12 Months of Age by Treatment Assignment for Infants

Data were only collected at 1, 3, 6, and 12 months. ELF indicates Early Limited Formula.

Effect of Treatment Assignment on Outcomes Adjusting for Potential Confounding Variables

Intended duration of breastfeeding and maternal marital status were unevenly distributed between the 2 groups at baseline by chance and were also associated in bivariate analysis with breastfeeding at 6 and 12 months and with time-to-event of breastfeeding cessation (eTable 2 in Supplement 2). In multivariable logistic regression also adjusting for stratification variables, adjusting for marital status attenuated the odds ratio for the effect of ELF on breastfeeding at 6 months from 0.56 (95% CI, 0.28-1.15) to 0.61 (95% CI, 0.27-1.40) and attenuated the odds ratio for the effect of ELF on breastfeeding at 12 months from 0.45 (95% CI, 0.23-0.89) to 0.55 (95% CI, 0.25-1.20). There was no interaction between treatment assignment and marital status, or between treatment assignment and planned duration of breastfeeding. Multivariable proportional hazards analysis adjusting for marital status and intended duration of breastfeeding as well as for the stratification variables found that the HR for ELF compared with control was 0.74 (95% CI, 0.48-1.14) with respect to time-to-event of breastfeeding cessation through 12 months. Maternal age, education, income, and site of enrollment were all strongly associated with time to breastfeeding cessation but did not differ by treatment assignment.

Relationship of Formula Feeding at 1 Week to Subsequent Breastfeeding Practices

Among 127 enrolled infants who responded to assessment of breastfeeding at 1 week of age, 38 of 60 infants in the ELF intervention group (63.3%) and 25 of 67 infants in the control group (78%)

had breastfed without formula for the past 24 hours (P = .08). The receipt of formula at 1 week of age was very strongly associated with all subsequent breastfeeding outcomes. At ages 6 and 12 months, respectively, 11 (31.4%) and 2 (5.7%) of 35 infants who had received formula in the past 24 hours at age 1 week were still breastfeeding, compared with 75 (85.2%) and 47 (53.4%) of the 88 who had not received formula in the past 24 hours at age 1 week. Thus, the risk differences for the effect of receiving formula at 1 week on the outcomes of breastfeeding prevalence at 6 months was –53.8 (95% CI, –70.9 to –36.7) and for 12 months, it was –46.9 (95% CI, –60.0 to –33.9). Receipt of formula at age 1 week was also associated with time-to-event of breastfeeding cessation (HR, 4.84; 95% CI, 3.00-7.78); this effect was noted among infants randomly assigned to ELF (HR, 3.37; 95% CI, 1.77-6.44) and even more pronounced among those randomly assigned to control (HR, 7.16; 95% CI, 3.51-14.6).

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Discussion

Using ELF in the first days after birth did not alter the prevalence of breastfeeding or formula use at 6 months of age in the ELF-TLC cohort of infants likely to breastfeed successfully, who were born in US academic institutions with strong breastfeeding support, and had a median breastfeeding duration of 9 months. However, infants randomly assigned to ELF had a lower prevalence of breastfeeding at 12 months of age than those assigned to the control intervention in unadjusted analyses. Owing to the uneven distribution of major predictors of breastfeeding cessation that occurred by chance at enrollment, it is unclear whether this observed deleterious association between ELF and breastfeeding at 12 months may be attributable to confounding. Nevertheless, our results do not provide evidence that ELF should be used for the goal of improving breastfeeding duration through 12 months in populations similar to those studied in ELF-TLC. It is unknown whether the effect of ELF on long-term breastfeeding prevalence might differ for populations at higher risk of early cessation.

Our finding that ELF did not affect breastfeeding prevalence through age 6 months but may have decreased breastfeeding prevalence at 12 months raises an important question regarding the mechanism of action for these observed relationships between early feeding and subsequent breastfeeding duration. Previous studies of the deleterious association between early formula and subsequent breastfeeding duration have suggested that the causal mechanism for this association related to increased infant satiety from receipt of formula and concomitant decreased infant breastfeeding demand, increased maternal milk stasis, and decreased maternal milk production.[5,6,7,26] However, this causal mechanism is not supported by the results from our trial, which demonstrated a relationship between ELF and breastfeeding at 12 months but not at earlier time points. The substantial majority of infants randomly assigned to ELF had discontinued ELF by age 1 week and were exclusively breastfeeding at that time. It is unlikely that the behavior of 6-month-old infants who received ELF briefly after birth followed by resumption of exclusive breastfeeding differed from the behavior of 6-month-old infants exclusively breastfed since birth. As a result, any effect of ELF on long-term breastfeeding could be attributable to an alteration in maternal or family behavior associated with the early use of formula. It is possible that using ELF in the newborn period reduces maternal or other family commitment to avoiding formula in later infancy, perhaps especially once complementary feeding has been initiated, and that greater use of formula in later infancy increases the risk of breastfeeding cessation before 12 months of age.

The mechanism by which ELF may have had a delayed, detrimental effect on long-term breastfeeding duration is important because for some infants, small volumes of formula can be beneficial in the neonatal period for ameliorating or precluding early morbidity such as hyperbilirubinemia or dehydration. One potential mechanism for a delayed deleterious effect of ELF on breastfeeding might be exposure of the parents to clinical counseling strategies in early infancy that assert the importance of a dichotomous, “virgin”[27] state with respect to formula, rather

than a more nuanced approach to supporting breastfeeding. Although exposure to specific clinical counseling strategies was not assessed in ELF-TLC, it is known that 58% of those who declined to enroll stated that they did not want to use formula for their infants; this suggests that the target population had been exposed to counseling against formula use. For mothers who either do choose or are required to use small volumes of formula in early infancy, previous exposure to a starkly dichotomous counseling strategy during routine clinical care could potentially dampen subsequent commitment to avoiding formula during later infancy and could therefore be a mechanism by which the early use of small volumes of formula leads to premature cessation of breastfeeding.

However, starkly dichotomous counseling regarding early formula use is not evidence based. Although many studies have shown a deleterious association between any formula use and subsequent breastfeeding outcomes,[28,29,30,31,32] the timing and the actual volume used may be a factor. Only a few studies have separated the effect of small volumes of formula from that of large volumes of formula,[2,15,16] and no studies that have specifically examined the effect of small volumes of formula have demonstrated any association with deleterious outcomes.[33] Our study's results are consistent with the possibility that ELF may have clinically significant benefits as well as risks for subsequent breastfeeding behavior. Counseling that implies a deleterious effect of small volumes of formula in the neonatal period is inaccurate and could be detrimental to long-term breastfeeding success.

When weighing the risks and benefits of formula use in early infancy, clinicians and parents may wish to consider ELF-TLC's results highlighting a potentially important role for formula use at age 1 week. Although an effect of ELF on breastfeeding at age 6 months was not demonstrated, the use of formula at 1 week had a negative association with breastfeeding outcomes at both 6 and 12 months. If formula is used in the first few days after birth to ameliorate hyperbilirubinemia or dehydration, the risks and benefits of formula use should be discussed, and if formula is used, it should be discontinued as soon as possible. Ongoing formula use at 1 week of age indicates a mother at high risk of early breastfeeding cessation.

Limitations

Our study has several important limitations. First, ELF-TLC enrolled newborns with weight loss at or above the 75th percentile but excluded newborns with weight loss of 10% or greater. Second, enrolled participants delivered in US academic medical centers with strong breastfeeding support, and although 67.9% of mothers were college graduates, 15% were younger than 25 years. Further research is needed to identify supplementation strategies supportive of breastfeeding for infants with weight loss of 10% or greater and in other settings. Third, 1 in 4 eligible mothers consented to enroll in ELF-TLC. Mothers who chose to enroll may have been ambivalent about whether formula would be beneficial to their infant, and so may not be representative of all mothers of newborns with pronounced weight loss.

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Conclusions

Breastfeeding prevalence at 6 months of age was not altered in our study population by the use of ELF in the newborn period. Given results previously released by the ELF trial suggesting that ELF may ameliorate neonatal morbidity, these new findings indicate that in settings with strong breastfeeding support and long duration of breastfeeding, ELF should be used in the early newborn period only when the beneficial effect on neonatal morbidity is expected to exceed any potential deleterious effect on long-term breastfeeding. Our findings also confirm that to minimize any potential deleterious effect on long-term breastfeeding, any formula initiated in the first few days should be discontinued as soon as possible and before 1 week of age. The results of ELF-

TLC may also reassure mothers and clinicians that most newborns who use formula in the first few days are able to discontinue its use by 1 week. Future research is needed to identify specific populations likely to receive net benefits from targeted early supplementation and to develop evidence-based criteria for the precise timing and amount of supplementation that will minimize newborn morbidity while improving long-term breastfeeding duration. Such criteria could potentially allow clinicians, parents, and hospitals to work together to optimize overall health outcomes during early infancy and beyond.

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Notes

Supplement 1.

Trial Protocol

Click here for additional data file.(2.1M, pdf)

Supplement 2.

eTable 1. Breastfeeding Prevalence at 6 and 12 Months Within Subgroups Unevenly Distributed at Baseline or Pre-specified and Within Each Site, by Treatment Assignment

eTable 2. Univariate and Multivariable Hazard Ratios (HR) for Demographic and Clinical Predictors Present at Birth, of Time to Breastfeeding Cessation Through Age 12 Months

Click here for additional data file.(91K, pdf)

Supplement 3.

Data Sharing Statement

Click here for additional data file.(17K, pdf)
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The Effect of Early Limited Formula on Breastfeeding, Readmission, and Intestinal Microbiota: A Randomized Clinical Trial

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Objective To determine whether using 10 mL formula after each breastfeeding before copious maternal milk production affects breastfeeding duration, readmission, and intestinal microbiota through 1 month of age.

Study design In this randomized controlled trial, we enrolled 164 exclusively breastfeeding newborns, 24-72 hours old, whose weight loss was ≥75th percentile for age, and whose mothers had not yet begun mature milk production. Enrolled newborns were assigned randomly to either supplement breastfeeding with early limited formula (ELF), 10 mL of formula after each breastfeeding stopped at the onset of copious maternal milk production (intervention), or to continue exclusive breastfeeding (control). Outcomes assessed through 1 month included breastfeeding duration, readmission, and intestinal microbiota.

Results At 1 week of age, 95.8% of infants receiving ELF and 93.5% of control infants were still breastfeeding ($P > .5$); readmission occurred for 4 (4.8%) control infants and none of the infants receiving ELF ($P = .06$). At 1 month of age, 86.5% of infants receiving ELF and 89.7% of control infants were still breastfeeding ($P > .5$); 54.6% of infants receiving ELF and 65.8% of controls were breastfeeding without formula ($P = .18$). ELF did not lead to decreased abundance of *Lactobacillus* or *Bifidobacterium* and was not associated with expansion of *Clostridium*.

Conclusion In this population of healthy newborns with weight loss ≥75th percentile, ELF did not interfere with breastfeeding at 1 month, breastfeeding without formula at 1 month, or intestinal microbiota. ELF may be an important therapeutic option for newborns with the potential to reduce readmission rates. *(J Pediatr 2018;196:84-90).*

Trial Registration Clinicaltrials.gov: NCT02313181.

Public health initiatives from the Centers for Disease Control and Prevention, the Surgeon General, and the World Health Organization have discouraged hospitals, providers, and parents from using formula for newborns during the birth hospitalization.[1-5] To support these initiatives, the Joint Commission established quality measures aimed at reducing the use of formula for breastfed newborns.[6-8] Since these measures were implemented in 2010, rates of exclusive breastfeeding have risen substantially in US hospitals.[3,9] However, rising rates of exclusive breastfeeding have presented clinical challenges in newborn management, doubling the risk of hyperbilirubinemia, dehydration, and readmission.[10-12] The increased risk is partly attributable to the low enteral intake of exclusively breastfed newborns in the first few days after birth, when mothers produce about 1-5 mL of colostrum per feeding.[13,14] Newborns with pronounced weight loss in the first few days are at high risk of hyperbilirubinemia and dehydration, perhaps because more pronounced weight loss is a marker of low enteral intake.[15-20]

Increasing enteral volume by supplementing breastfed newborns with formula could ameliorate morbidity, especially for those with pronounced weight loss, but has been discouraged by guidelines as the result of several concerns. First, numerous studies have demonstrated that receiving both breast milk and formula in the first few days after birth increases the risk of breastfeeding cessation.[21-26] Second, some evidence suggests that the use of formula along with breastfeeding reduces the health benefits associated with breastfeeding, perhaps by altering the abundance of beneficial intestinal microbiota such as *Lactobacillus* and *Bifidobacterium*, which have been associated with reduced risk of infectious and allergic disease.[27-32] Some studies have also reported that the use of formula increases the abundance of taxa such as *Clostridia* that are associated with increased risk of eczema.[33-35] Third, the use of formula to supplement breastfeeding can impact maternal experience. If formula feeding is perceived by mothers as easier or "better" than breastfeeding, this may impact maternal breastfeeding self-efficacy.[36-38] Citing

BSES-SF	Breastfeeding Self-Efficacy Scale–Short Form
ELF	Early limited formula
ELF-TLC	Early Limited Formula for Treating Lactation Concerns
EPDS	Edinburgh Postnatal Depression Scale
SMNHC	Satisfaction with Maternal and Newborn Health Care Following Childbirth
STAI-SS	State Trait Anxiety Inventory (State Subscale)
UCSF	University of California San Francisco

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these concerns, current guidelines recommend avoiding supplementation and continuing exclusive breastfeeding even in the setting of pronounced weight loss, unless supplementation is determined to be medically necessary.[39,40]

Each year, about 80 000 newborns in the US require readmission after discharge from the birth hospitalization.[11,41] The majority of these neonatal readmissions are related to hyperbilirubinemia or dehydration, 2 conditions potentially ameliorated by formula supplementation.[11,12,41] Developing a strategy to balance the beneficial effect of formula on dehydration and hyperbilirubinemia while avoiding any detrimental effect on maternal experience, on breastfeeding duration, or on the presence of key intestinal taxa such as *Lactobacillus*, *Clostridium*, and *Bifidobacterium* might improve newborn outcomes.

In a small randomized trial, our group previously studied the use of early limited formula (ELF), a strategy using 10 mL of extensively hydrolyzed formula fed via syringe after each breastfeeding and discontinued after the onset of copious maternal milk, and reported that ELF improved rates of breastfeeding and of breastfeeding without formula at 3 months.[42] Other existing studies regarding the impact of formula on the short-term and long-term risks and benefits of breastfeeding have not specifically examined the impact of small volumes of formula, administered during the period of low maternal milk volumes, followed by the resumption of exclusive breastfeeding. Our study, Early Limited Formula for Treating Lactation Concerns (ELF-TLC), was designed to test the hypothesis that the ELF approach improves length of breastfeeding duration for infants with pronounced weight loss compared with the currently recommended strategy of continued exclusive breastfeeding.

Methods

Between January 2015 and September 2016, ELF-TLC enrolled healthy, exclusively breastfeeding term (≥37 week) singletons born at the University of California San Francisco (UCSF) Medical Center (San Francisco, California) and at Penn State Milton S. Hershey Medical Center (Hershey, Pennsylvania). We included infants with weight loss ≥75th percentile on The Newborn Weight Tool (www.newbornweight.org) whose mothers had not yet begun copious milk production.[43] We excluded infants with birth weight <2500 g, those the clinical team had recommended should not breastfeed, and those who had received formula, required a greater level of care than a Level 1 nursery, had mothers who were <18 years old or could not speak English, were not expected to be discharged home with their parents, or were observed for narcotic abstinence syndrome. We also excluded infants who had lost ≥10% of their birth weight because such infants routinely were supplemented in both enrolling institutions. Weight measurement obtained during routine hospital care was used to determine eligibility for enrollment. A study nurse obtained informed consent from mothers for themselves and their infant. The ELF-TLC trial was approved by the UCSF Committee on Human Research, the Human Subjects Protection Office at Penn State College of Medicine, and the University of California Davis institutional review board and is registered at clinicaltrials.gov (ClinicalTrials.gov: NCT02313181).

We randomly assigned 164 mother–infant pairs either to breastfeed with ELF or to continue exclusive breastfeeding with a safety control intervention. An independent biostatistician generated the randomized allocation sequence using a password-encoded Excel spreadsheet (Microsoft Corporation, Redmond, Washington) stratified on location and on method of delivery. A study nurse accessed this sequence following enrollment to determine treatment assignment.

All study nurses at both sites received training from the Principal Investigator before the study commencement and at the midpoint of enrollment. Immediately after enrollment and treatment assignment, all mothers breastfed with support from a study nurse. After this supported breastfeeding, mothers randomly assigned to ELF were taught to feed their infants 10 mL of formula using a feeding syringe after each breastfeeding until the onset of copious breast milk. Extensively hydrolyzed formula (Nutramigen; Mead Johnson Nutrition, Inc, Glenview, Illinois) was used for the intervention because of the reported beneficial effect of extensively hydrolyzed formula on bilirubin levels[44] and because our pilot study indicated its color, odor, and expense might help families distinguish it from standard cow's milk formulas.[42] Mothers randomly assigned to the control group were instructed to continue exclusive breastfeeding as recommended by existing guidelines unless directed by a healthcare provider to begin formula and/or discontinue breastfeeding. Mothers assigned to the control group were taught infant safety techniques (including household water temperature, car seat position, and safe infant sleep environment) for 15 minutes by the study nurse to reduce any confounding by providing an equal amount of time and attention to control participants and ELF participants.

The enrolling nurse surveyed all mothers for covariates related to breastfeeding, including maternal country of birth, previous breastfeeding experience, race/ethnicity, and planned duration of breastfeeding and also assessed measures including the Breastfeeding Self-Efficacy Scale–Short Form (BSES-SF), the State Trait Anxiety Inventory (State Subscale) (STAI-SS), the Edinburgh Postnatal Depression Scale (EPDS), and the Satisfaction with Maternal and Newborn Health Care Following Childbirth (SMNHC).[38,45-47] All infants received usual care before and subsequent to the study nurse visit at enrollment.

A research assistant blinded to study group assignment assessed 1-week and 1-month outcomes via telephone call, including the outcomes of continued breastfeeding with and without formula, neonatal readmission, STAI-SS, and EPDS. In addition, at 1 week the research assistant verbally administered the BSES-SF and SMNHC. A score of ≥40 on the STAI-SS was defined as a positive screen for anxiety, and a score of ≥12 on the EPDS was defined as a positive screen for depression, as was any answer other than "never" to the EPDS item querying mothers about self-harm. Screening tests were scored within 24 hours of survey administration, and positive screens were reported by study staff to the mother's obstetric team or primary care provider.

ELF-TLC assessed breastfeeding status at 1 week and 1 month using the item, "Has your baby breastfed or received any breast milk in the past 24 hours?" ELF-TLC assessed breastfeeding without formula at 1 week and 1 month using the item, "In the past 24 hours, how often was your baby fed formula?" We assessed overall duration of exclusive breastfeeding using the item, "Has your child received anything other than breast milk?" To gain a better understanding of adherence to the ELF technique among those assigned to ELF, we used semirandom sampling (first enrollment of the month) to query 18 mothers randomly assigned to ELF about their adherence to the ELF protocol.

We used χ^2 testing to assess associations between study group and breastfeeding status and to examine this association for infants enrolled at each site. We used the Fisher exact test to assess the association between study group and neonatal readmission. We used the Student *t* test to compare the effect of ELF to control with respect to continuous outcomes including BSES-SF total score, STAI-SS total score, and SMNHC. All analyses were intention-to-treat and were conducted in Stata 14.1 (StataCorp LLC, College Station, Texas).

Stool specimens from 15 infants (8 in the ELF group and 7 in the control group) were collected from a convenience sample for the exploratory aim of this study. For these 15, we collected and analyzed intestinal microbiota at enrollment (baseline), 1 week, and 1 month of age using Norgen stool nucleic acid preservation tubes (Norgen Biotek, Thorold, Canada). Total bacterial composition was assessed by 16S rRNA gene sequencing using the UC Davis Host-Microbe Systems Biology Core. Bacterial 16S ribosomal RNA variable region 3/4 sequences were amplified with region-specific barcoded polymerase chain reaction primers and sequenced on the Illumina MiSeq platform (Illumina, Inc, San Diego, California). Computational analysis used metagenomic pipelines using Quantitative Insights Into Microbial Ecology (ie, QIIME).[48,49] We used linear mixed-effect modeling with the lme4 package in R (R Foundation for Statistical Computing, Vienna, Austria) to examine differences in microbial abundance longitudinally between treatment groups. Because the results of our linear mixed-effect modeling were not significant, we compared the 2 treatment groups with respect to specific taxa using the Wilcoxon rank-sum test at 1 week and 1 month. To control for multiple comparisons, we used the qvalue package in R to assess false discovery rate. No differences met $q < 0.1$, so *P* values are shown in **Figure 1** (available at www.jpeds.com). We used principal component analysis to examine the global environment of microbiota and report how each sample related to other samples with respect to the global environment. Diversity statistics were calculated using the *vegan* package in R. All plots were made in ggplot2 in R.

ELF-TLC's sample size of 164 was chosen to achieve 90% power ($\alpha = 0.05$) to detect a relative risk of 1.4 between the 2 groups with respect to the proportion breastfeeding at 6 months of age, an effect size similar to that identified in the existing literature.[21,23,29,50-55] The sample size of 164 infants also was planned to give the study 90% power ($\alpha = 0.05$) to detect a difference of 5 points between the groups with respect to STAI-SS at 1 week and 1 month and a difference of 4 points between the groups with respect to SMNHC at 1 month. ELF-TLC's prespecified primary outcome was length of breastfeeding duration. The prespecified secondary outcomes were STAI-SS score, neonatal healthcare use, and formula use through 1 month of age. Additional prespecified outcomes included EPDS, BSES-SF, and SMNHC scores.

Intestinal microbiota outcomes were not prespecified because of the exploratory nature of this aim. Given the size of the cohort for the assessment of intestinal microbiota (8 infants in the ELF group and 7 infants in the control group), our analyses had 80% power to detect effect sizes of 1.56 SDs.

Results

We enrolled 164 mother–infant dyads in this randomized trial; **Table I** lists characteristics of enrolled dyads. Compared with controls, mothers assigned to ELF were less likely to be married and had a slightly shorter intended duration of breastfeeding; otherwise, there were no baseline differences between the groups. Mothers randomly assigned to ELF used ELF 5.4 ± 3.0 times per day for a median of 2 days (IQR 1-4 days, range 1-7 days). We ascertained outcomes for 152 (92.7%) infants at 1 month; loss to follow-up at 1 month did not differ by treatment assignment (**Figure 2**).

Breastfeeding rates at 1 week did not differ by treatment assignment; 95.8% of infants receiving ELF were still breastfeeding, compared with 93.6% of controls ($P = .54$). The risk ratio for the effect of ELF on the outcome of breastfeeding prevalence at 1 week of age was 1.02 (confidence interval 0.16-2.62). Among control participants, 28 (37.3%) received some formula by 1 week of age, and at 1 week of age, 15 (22%) of control participants had received formula within the past 24 hours. At 1 week of age, control newborns receiving formula received 13.7 ± 10.6 fl oz per day and newborns receiving ELF received 10.2 ± 9.6 fl oz per day ($P = .32$). Treatment assignment did not correlate with breastfeeding self-efficacy scores, maternal satisfaction with healthcare, postpartum depression, or state anxiety (**Table II**). In the first week, 4 control infants were readmitted to the hospital (3 for hyperbilirubinemia and 1 for which reason for readmission was not provided), and no infants receiving ELF were readmitted ($P = .06$).

Breastfeeding outcomes at 1 month did not differ by treatment assignment; 86.5% of infants receiving ELF were still breastfeeding compared with 89.7% of controls ($P = .53$). The risk ratio for the effect of ELF on the outcome of breastfeeding cessation by 1 month of age was 1.21 (confidence interval 0.55-3.16). Among the subgroup of infants enrolled at UCSF, breastfeeding prevalence at 1 month was 100% among those assigned to ELF and 97.6% among the control group ($P = .35$); among the subgroup of infants enrolled at Penn State, breastfeeding prevalence at 1 month was 73.7% among infants receiving ELF and 81.1% among the control group ($P = .44$). Among control participants, 43 (57.3%) had received some formula by 1 month of age. Current breastfeeding without formula at 1 month did not differ by treatment assignment; 65.8% of controls had received no formula in the past 24 hours,

Table I. Demographic and clinical characteristics at enrollment for infants randomly assigned to ELF or to continued exclusive breastfeeding (control)

Characteristics	ELF group (intervention) (n = 82)	Continued exclusive breastfeeding (control) (n = 82)	*P* value
Gestational age, wk, mean ± SD	39.4 ± 1.2	39.4 ± 1.1	.69
Vaginal delivery, n (%)	61 (74.4)	60 (73.2)	.86
Infant age at enrollment, h, mean ± SD	35.7 ± 9.5	36.1 ± 9.0	.77
Maternal age, y, mean ± SD	31.3 ± 5.6	31.6 ± 6.2	.74
Maternal race-ethnicity, n (%)			.82
White non-Hispanic	57 (70.4)	57 (69.5)	
Black non-Hispanic	3 (3.7)	2 (2.4)	
Hispanic	10 (12.3)	10 (12.2)	
Asian	9 (11.1)	8 (9.8)	
Other	2 (2.5)	5 (6.1)	
Mother completed college	52 (63.4)	58 (70.7)	.32
Married, n (%)	53 (66.3)	66 (81.5)	**.03***
Primiparous, n (%)	51 (63.0)	48 (58.5)	.56
Percent weight loss, mean ± SD	6.3 ± 1.6	6.4 ± 1.5	.55
Birth weight, g, mean ± SD	3372.5 ± 669.6	3397.7 ± 453.1	.78
US born, n (%)	66 (82.5)	66 (81.5)	.87
Mother with breastfeeding experience, n (%)	32 (39.5)	31 (38.3)	.87
Planned breastfeeding duration, mo, mean ± SD	8.6 ± 3.4	9.9 ± 4.4	**.049**
BSES-SF score, mean ± SD	47.7 ± 8.8	46.8 ± 10.4	.58

Values in bold indicate $P < 0.05$ (statistically significant).

compared with 54.6% of the ELF group ($P = .18$). In total in the first month, 1 infant receiving ELF was readmitted for hyperbilirubinemia, and 5 control infants were readmitted (3 for hyperbilirubinemia, 1 for umbilical infection, and 1 for which reason for readmission was not provided). Maternal age, education, parity, intended duration of breastfeeding, income, country of birth, and site of enrollment all strongly predicted breastfeeding rates through 1 month, although treatment assignment did not predict this outcome (**Table III**).

All participants showed large shifts in microbial abundance between enrollment and 1 week of age and between 1 week of age and 1 month of age (**Figure 1**, A). For example, abundances of *Actinomyces* and *Prevotella* declined over the first month of life (**Figure 1**, B). The use of ELF did not reduce the

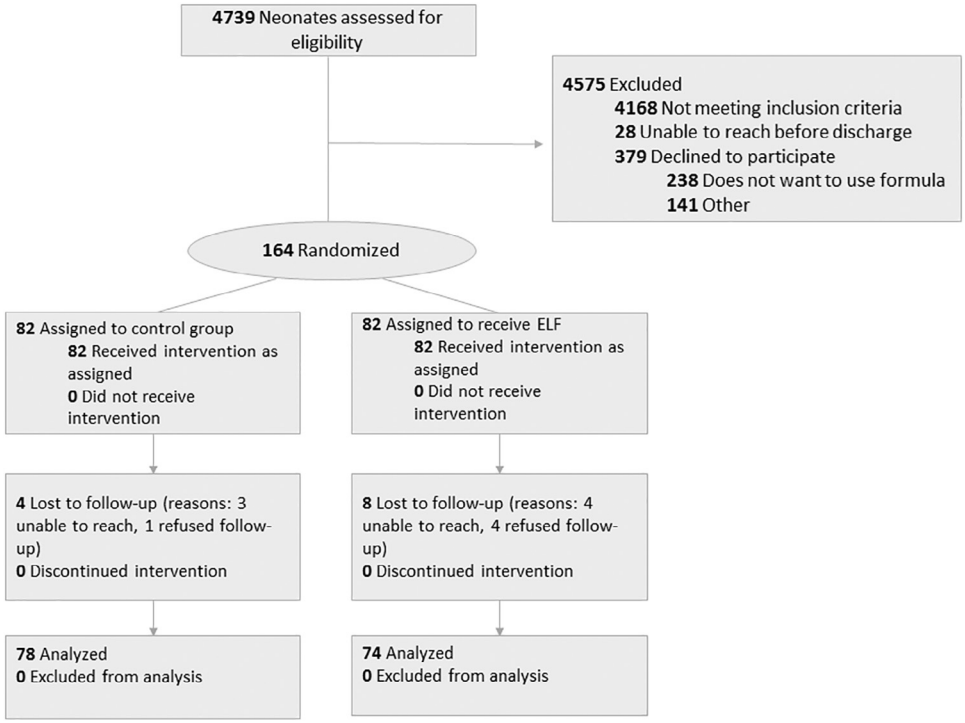

Figure 2. Cohort derivation (CONSORT diagram).

Table II. Breastfeeding duration, formula use, and maternal experience through 1 month of age, by treatment assignment

Outcomes	ELF group (intervention) (n = 82)	Continued exclusive breastfeeding (control) (n = 82)	*P* value
Breastfeeding at 1 wk, n (%)	69 (95.8)	73 (93.6)	.54
Breastfeeding, at 1 mo, n (%)	64 (86.5)	70 (89.7)	.53
Formula use in past 24 h at 1 wk, n (%)	22 (36.7)	15 (22.4)	.08
Formula use in past 24 h at 1 mo, n (%)	30 (45.5)	25 (34.3)	.18
BSES-SF score at 1 wk, mean ± SD	52.6 ± 8.6	52.3 ± 11.5	.87
EPDS score at 1 wk, mean ± SD	4.7 ± 3.3	4.4 ± 3.9	.61
STAI-SS score at 1 wk, mean ± SD	29.0 ± 7.1	28.6 ± 8.7	.76
Positive EPDS screen at 1 wk, n (%)	3 (4.7)	5 (7.4)	.41
Positive STAI-SS screen at 1 wk, n (%)	5 (7.9)	11 (16.4)	.14
EPDS score at 1 mo, mean ± SD	4.2 ± 3.6	3.4 ± 3.1	.13
STAI-SS score at 1 mo, mean ± SD	28.5 ± 8.6	27.3 ± 8.1	.39
Positive EPDS screen at 1 mo, n (%)	3 (4.5)	2 (2.7)	.58
Positive STAI-SS score at 1 mo, n (%)	7 (10.8)	7 (9.7)	.84
Modified SMNHC score, n (%)	45.7 ± 7.9	47.7 ± 6.7	.12

abundance of *Lactobacillus* or increase the abundance of *Clostridia* in this cohort (**Figure 1**, C). In principal component analysis, ELF did not have sufficient impact to cause separation of control vs treated subjects at any time point. We used the corresponding loadings to determine the taxa that contributed most toward microbiota variation, including unclassified Enterobacteriaceae and *Bacteroides*. Plotting samples based on the abundances of these taxa showed that ELF did not have sufficient impact to cause separation of control vs treated subjects at any time point (**Figure 1**, D). There were no differences in Shannon diversity associated with delivery mode, treatment, or time point.

Discussion

Current public health initiatives emphasize the importance of exclusive breastfeeding during the birth hospitalization, but our randomized trial of 164 newborns did not demonstrate improved outcomes for infants receiving exclusive breastfeeding compared with limited formula supplementation using the ELF strategy. Furthermore, ELF did not affect breastfeeding duration or formula use in the first month and did not impact microbial diversity or lead to decreased abundance of *Lactobacillus* or *Bifidobacterium* or expansion of *Clostridium*. These findings are important because increasing enteral intake for newborns with pronounced weight loss might reduce morbidity from jaundice and dehydration and could lead to reduced newborn readmissions. We also found that ELF was used for a median (IQR) of 2[1-4] days; during the first week, there were no readmissions for newborns assigned to ELF, and 4 readmissions occurred for control newborns.

In contrast to existing observational studies,[21-26] the results of the current randomized trial showed no impact of ELF on breastfeeding outcomes, even though unmarried mothers and those with shorter intended breastfeeding duration were overrepresented in the ELF vs the control group. Two factors may help explain our findings. First, the structured, temporary

Table III. Clinical and demographic predictors of breastfeeding at 1 month

Clinical and demographic factors	Breastfeeding at 1 mo (n = 134)	Not breastfeeding at 1 mo (n = 18)	*P* value
Vaginal delivery, n (%)	103 (76.9)	12 (66.7)	.34
Infant age at enrollment, h, mean ± SD	36.2 ± 9.2	34.7 ± 10.5	.52
Maternal age, y, mean ± SD	31.8 ± 5.6	28.6 ± 6.3	**.02**
Primiparous, n (%)	86 (64.2)	7 (38.9)	**.04**
Maternal race-ethnicity, n (%)			.22
White non-Hispanic	87 (64.9)	16 (88.8)	
Black non-Hispanic	4 (3.0)	1 (5.6)	
Hispanic	19 (14.2)	1 (5.6)	
Asian	17 (12.7)	0 (0.0)	
Other	7 (5.2)	0 (0.0)	
Percent weight loss at enrollment, mean ± SD	6.4 ± 1.5	6.1 ± 1.7	.44
US born, n (%)	104 (78.8)	18 (100.0)	**.03**
Pennsylvania enrollment, n (%)	58 (43.3)	17 (94.4)	**<.001**
Previous breastfeeding experience, n (%)	50 (37.6)	8 (44.4)	.58
Planned breastfeeding duration, mo, mean ± SD	9.5 ± 3.8	7.8 ± 3.7	.09
Baseline BSES-SF score, mean ± SD	47.8 ± 9.4	41.2 ± 10.5	**.006**
College graduate, n (%)	98 (73.1)	7 (38.9)	**.003**
Married, n (%)	101 (76.5)	10 (55.6)	.06
Income ≥$50 000, n (%)	99 (79.2)	6 (40.0)	**.001**

Values in bold indicate $P < 0.05$ (statistically significant).

approach of ELF may differ from the usual approach to formula supplementation. By offering a limited volume of formula, fed by syringe rather than bottle, and instructing mothers to discontinue formula at the onset of mature milk production, ELF may offer the benefits of supplementation without satiating newborns or causing nipple confusion and may support continued successful breastfeeding. The limited volume and temporary nature of ELF also may preclude any lasting impact of supplementation on intestinal microbiota. Second, previous studies showing an association between early formula use and early breastfeeding discontinuation have been observational.[21-23,25] Randomized trials have not demonstrated any adverse effect of supplementation on breastfeeding duration.[42,56,57] It is therefore possible that the numerous observational studies in this area were affected by confounding.

Although ELF did not interfere with breastfeeding outcomes, our results suggest that ELF reduces a newborn's risk of morbidity leading to hospital readmission. In our cohort, 6 of 164 infants (3.7%) were readmitted in the first month. The ELF-TLC inclusion criteria of newborns exclusively breastfeeding with weight loss ≥75th percentile may have identified a population at greater risk of morbidity leading to readmission. Mothers randomly assigned to ELF were able to implement the intervention after an initial brief counseling session. Thus, if using ELF reduces morbidity in this greater-risk population without interfering with breastfeeding duration, ELF could be a practical therapeutic option for mothers and babies to support a healthy transition from hospital to home. Currently, quality measurement organizations such as the Joint Commission and the Baby Friendly Hospital Initiative discourage any supplementation strategies for breastfed newborns; thus, any formula use for breastfed newborns detracts from hospital quality scores. Based on the results of ELF-TLC, revising such quality measures to permit use of ELF for infants meeting criteria might reduce the risk of neonatal readmission.

Our study has several important limitations. First, only 1 in 4 eligible mothers consented to enroll in ELF-TLC. Mothers who chose to enroll were open to either continuing exclusive breastfeeding or initiating limited supplementation with formula. Second, there were few African American mothers in our enrolled cohort, and only 15% of mothers were <25 years old. For this reason, the generalizability of our results to these groups is unknown. Because the risk of breastfeeding cessation is elevated for African American mothers and for mothers <25 years old, future studies should examine the effectiveness of ELF for these groups. Alternatively, we had good participation by white non-Hispanic, Hispanic, and Asian mothers. Third, intestinal microbiota were sampled from only a subset of infants from 1 site and were followed for only 1 month. Although studies of intestinal microbiota often attain adequate power from small sample sizes, further research in this area will be needed to definitively determine the effect of ELF on the microbiome. Fourth, ELF-TLC enrolled only newborns with weight loss ≥75th percentile for age; our results therefore do not apply to newborns with less pronounced weight loss. Many newborns tolerate the first few days of weight loss quite well and may not receive any benefit from ELF.

In conclusion, these results suggest that using ELF in a carefully structured, temporary manner may not interfere with breastfeeding or maternal experience in the first month or have a negative impact on intestinal microbiota. At the same time, our results suggest that further studies are needed to assess whether ELF reduces the risk of neonatal readmission, especially in the first week after birth. Using small volumes of formula on a temporary basis for newborns with pronounced weight loss may have the potential to help clinicians and mothers provide the nutritional volume needed by babies without interfering with duration of breastfeeding or with the health benefits achieved from longer breastfeeding duration. ■

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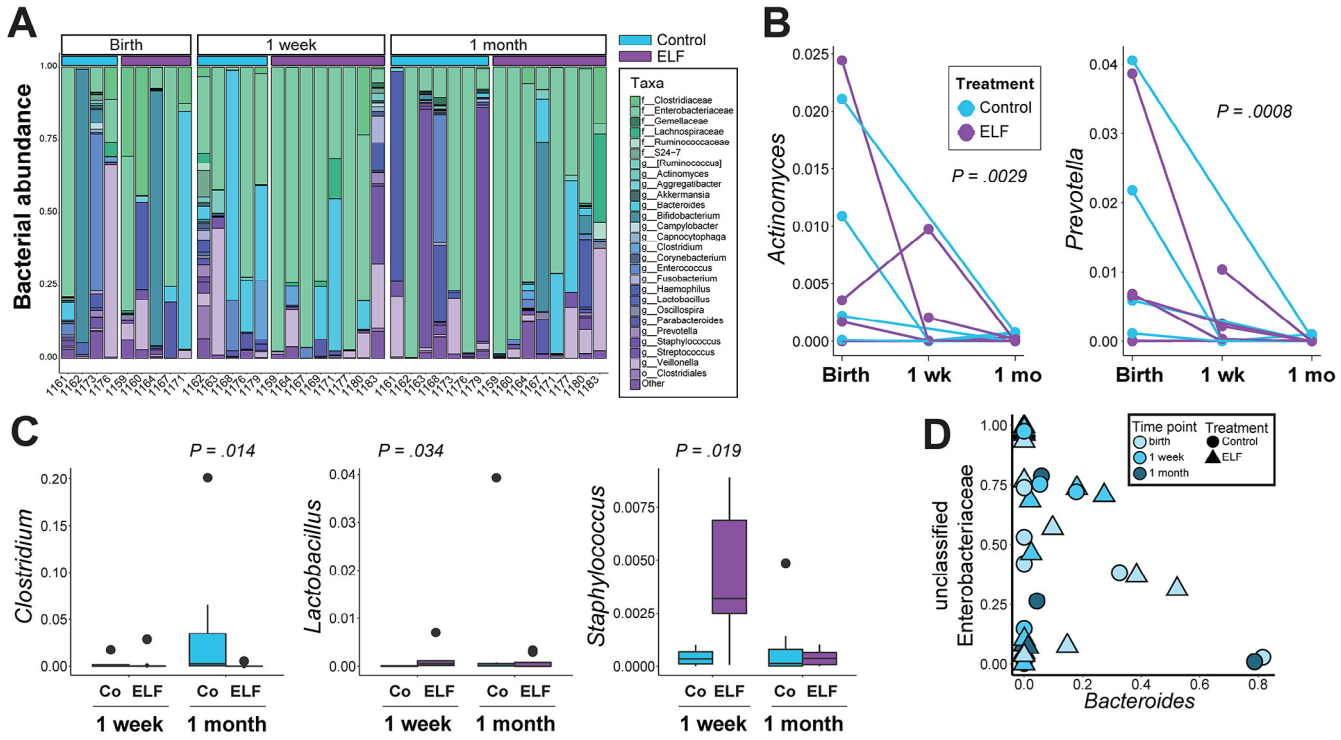


Figure 1. Intestinal microbiota at enrollment, 1 week, and 1 month after birth for newborns enrolled while exclusively breastfeeding and randomly assigned to either ELF (intervention) or continued exclusive breastfeeding (control). **A,** Abundances by genus; **B,** abundance of *Actinomyces* and *Prevotella* over the first month in ELF and control participants; **C,** abundance of *Clostridium*, *Lactobacillus*, and *Staphylococcus* at 1 week and 1 month in ELF and control groups; and **D,** abundances of unclassified Enterobacteriaceae and *Bacteroides* in infants receiving ELF and control infants. *Co*, control.

University of California
San Francisco

Human Research Protection Program
Committee on Human Research

Notification of Full Committee Approval

Principal Investigator
Valerie J Flaherman, MD

Co-Principal Investigator

Type of Submission: Initial Review Submission Packet
Study Title: The Early Limited Formula (ELF) Study

IRB #: 14-13484
Reference #: 086999

Reviewing Committee: Laurel Heights Panel

Study Risk Assignment: Minimal

Approval Date: 06/14/2014 **Expiration Date:** 06/13/2015

Regulatory Determinations Pertaining to This Approval:
The full committee determined that the research, which involves randomization to an "early limited formula" intervention or control group, and completion of questionnaires, poses no greater than minimal risk and is eligible for expedited review in the future under category #7.

This research satisfies the following condition(s) for the involvement of children:
45 CFR 46.404, 21 CFR 50.51: Research not involving greater than minimal risk.

Parental Permission and Assent:
The permission of one parent or guardian is sufficient.

The research meets conditions of 45 CFR 46.205 for the involvement of neonates.

Individual Research HIPAA Authorization is required of all subjects. Use the Permission to Use Personal Health Information for Research form.

A waiver of HIPAA Authorization and consent is acceptable for the recruitment procedures to identify potential subjects. The recruitment procedures involve routine review of medical or other records, do not adversely affect the rights and welfare of the individuals, and pose minimal risk to subjects and their privacy, based on, at least, the presence of the following elements: (1) an adequate plan to protect the identifiers from improper use and disclosure; (2) an adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, or a health or research justification for retaining the identifiers was provided or such retention is otherwise required by law; (3) adequate written assurances that the requested information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the requested information would be permitted by the Privacy Rule; (4) the research could not practicably be conducted without the waiver; and (5) study recruitment could not practicably be conducted without access to and use of the requested information. The

research subjects will sign a consent form prior to participation in the study.

IRB Comments:
Please submit the letter of support from the manager of the patient care unit as soon as it is available. It can be submitted as an Administrative Modification. Research activities should not begin on the patient care unit until you've obtained the letter of support.

All changes to a study must receive CHR approval before they are implemented. Follow the modification request instructions. The only exception to the requirement for prior CHR review and approval is when the changes are necessary to eliminate apparent immediate hazards to the subject (45 CFR 46.103.b.4, 21 CFR 56.108.a). In such cases, report the actions taken by following these instructions.

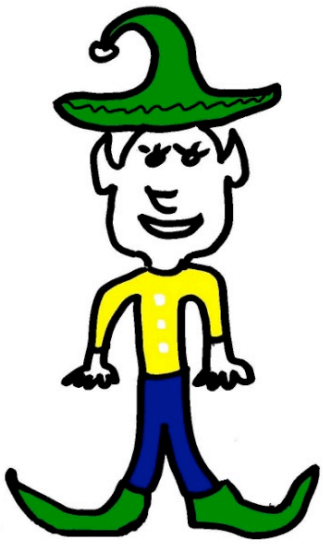
Expiration Notice: The iRIS system will generate an email notification eight weeks prior to the expiration of this study's approval. However, it is your responsibility to ensure that an application for continuing review approval has been submitted by the required time. In addition, you are required to submit a study closeout report at the completion of the project.

Approved Documents: To obtain a list of documents that were approved with this submission, follow these steps: Go to My Studies and open the study – Click on Submissions History – Go to Completed Submissions – Locate this submission and click on the Details button to view a list of submitted documents and their outcomes.

For a list of all currently approved documents, follow these steps: Go to My Studies and open the study – Click on Informed Consent to obtain a list of approved consent documents and Other Study Documents for a list of other approved documents.

San Francisco Veterans Affairs Medical Center (SFVAMC): If the SFVAMC is engaged in this research, you must secure approval of the VA Research & Development Committee in addition to CHR approval and follow all applicable VA and other federal requirements. The CHR website has more information.

The Early Limited Formula Treating Lactation Concerns (ELF-TLC) Study



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Funded by the United States Department of Health and Human Services (DHHS), Health Resources and Services Administration (HRSA), Maternal and Child Health Bureau (MCHB)
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The University of California at San Francisco
Penn State Hershey Children's Hospital

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I. PRINCIPAL HYPOTHESES TO BE TESTED

Breastfeeding provides many important health benefits to mothers and babies, and longer duration of breastfeeding is associated with much greater health benefits. However, the large majority of mothers and babies who begin breastfeeding shortly after birth actually stop breastfeeding well before the recommended duration of 12 months. Early breastfeeding problems occurring in the first few days after birth can have a major impact on overall breastfeeding duration. Weight loss is one such problem and can be rapid. In this study, we define rapid early weight loss as weight loss ≥75th percentile at the most recent weight as defined by an hourly nomogram demonstrating weight loss percentiles for exclusively breastfed newborns during the birth hospitalization. The PI of this study has previously shown that the brief, temporary use of small amounts of formula was helpful for infants with rapid early weight loss in overcoming early breastfeeding problems, and may allow these to continue breastfeeding through at least 3 months. The proposed research will build on this previous work and prospectively evaluate the impact of a small, controlled amount of Early, Limited Formula (ELF) on breastfeeding duration for mothers and newborns in a randomized controlled trial involving 164 mother-infant breastfeeding dyads. ELF may help mothers and babies transition through the brief period of early low milk production into successful, long-term breastfeeding. Our study will also report the effect of ELF on maternal experience including anxiety and depression and will examine the effect of ELF on healthcare utilization when compared with current standard of care, continued exclusive breastfeeding.

A. Proposed Hypotheses: For babies 18-72 hours old with rapid early weight loss, we hypothesize that the temporary use of 10 mL of formula fed by syringe immediately after each breastfeeding prior to the onset of mature milk production will improve breastfeeding duration and maternal experience and reduce overall healthcare utilization.

Outcomes to be studied for newborns include:

Primary outcome:
- Any breastfeeding at 6 months

Secondary outcomes:
- Any breastfeeding at various time points through 12 months
- Predominant breastfeeding >80% as defined by the Infant Feeding Practices II Study
- Any feeding other than breast milk at various time points through 6 months
- Volume of formula used in the past 24 hours at 1, 3 and 6 months of age

Outcomes to be studied for mothers include:
- Anxiety
- Breastfeeding self-efficacy
- Milk supply concern
- Parenting self-efficacy
- Postpartum depression

Outcomes to be studied for the health care system include:
- Infant office visits, emergency room visits and re-hospitalizations in the first month
- Maternal satisfaction with the quality of care in the first month

Additionally, we expect that ELF will have particularly positive effects on breastfeeding duration for mothers who are low-income and are therefore at higher risk of breastfeeding discontinuation. A subgroup analysis will be performed specifically for this population.

Specific hypotheses include:

- **Primary hypothesis:** ELF improves rates of any breastfeeding at 6 months.
- **Additional hypotheses:** ELF improves rates of any breastfeeding at 12 months.
- ELF improves predominant breastfeeding at 3 and 6 months.
- ELF improves rates of breastfeeding without concurrent formula at 3 months.
- ELF improves rates of breastfeeding without concurrent formula at 3 months for low-income mothers with household incomes <200% of the Federal Poverty Level
- ELF reduces the total volume of formula used in the first week.
- ELF reduces maternal state anxiety at 1 week.
- ELF ameliorates maternal milk supply concern.
- ELF improves maternal breastfeeding self-efficacy and parenting self-efficacy.
- ELF reduces the frequency of postpartum depression.
- ELF reduces health care utilization in the first month after birth.
- ELF improves maternal satisfaction with quality of care.

II. BACKGROUND AND RATIONALE

A. Introduction

National Breastfeeding Targets For Initiation Have Been Met, but Breastfeeding Rates at All Time Points After Initiation Are Lagging. Breastfeeding reduces infant morbidity and mortality[1-6] and benefits maternal health by reducing the incidence of breast[7] and ovarian cancer.[8] Longer duration of breastfeeding improves all these outcomes.[9, 10] At least 12 months of breastfeeding are recommended by the Centers for Disease Control and Prevention (CDC), the World Health Organization (WHO) and the American Academy of Pediatrics (AAP),[11-13] and Healthy People 2020 includes national breastfeeding goals at 0, 3, 6 and 12 months of age.[14] Healthy People 2020's target for breastfeeding initiation is 75%, and it is being met, with 76% of U.S. mother-infant pairs initiating breastfeeding.[13, 15, 16] However, most discontinue breastfeeding far before recommended: only 49% breastfeed through 6 months, and only 27% breastfeed through 12 months.[16, 17] Rates of breastfeeding are even lower for low-income U.S. mothers, with only 33% of low-income mothers breastfeeding at 6 months.[18]

Initial Physiologically Low Volumes of Milk Can Trigger a Cascade That May Lead to Breastfeeding Discontinuation. Immediately after birth, mothers begin production of early milk called colostrum that is high in nutrient concentration but very low in volume. Since each colostrum feeding averages 1-5 mL,[19, 20] exclusively breastfed newborns typically lose weight until copious mature milk production begins at about 2-5 days of age.[21, 22] While this weight loss generally does not cause serious medical problems, it can nevertheless raise maternal levels of anxiety, often even if clinicians have provided appropriate reassurance and education.[23-26] This is important because high levels of maternal anxiety in the postpartum period substantially increase the risk of breastfeeding discontinuation.[27] Furthermore, concerns about breastfeeding on day-of-life 3 also substantially increase risk of discontinuation.[28] Therefore, although newborn weight loss may not cause immediate medical consequences, it may risk generating a train of events that can end in breastfeeding discontinuation.

Hospitals Discourage Formula Use for Those Attempting to Breastfeed. Formula can ameliorate weight loss for newborns,[21, 22, 29] but using formula for breastfed newborns has been strongly associated with reduced breastfeeding duration in multiple observational studies.[9, 30-39] For this reason, current public health efforts have focused on discharging newborns with no formula use, whatsoever.[11, 40-44] The CDC,[13] the Surgeon General,[40] the WHO's Baby Friendly Hospital Initiative and the Joint Commission's Perinatal Care Core measure all promote discharging newborns without any formula use.[11, 41-44] Local and state agencies have been encouraging both academic and community hospitals to increase rates of exclusive breastfeeding during the birth hospitalization,[45-50] and rates of in-hospital formula supplementation have been falling across the nation.[51-55] However, since the evidence supporting these policies is observational,[9, 30-39] it is likely to have some confounding.[56] Mother-baby pairs with a greater determination to breastfeed would be less likely to use

formula and more likely to continue breastfeeding, and mother-baby pairs with latch or nipple problems would be more likely to use formula and less likely to continue breastfeeding.

The experimental evidence in this area has been limited, in part due to the difficulty in randomizing newborns to alternative feeding approaches.[57] *The only published clinical trial of formula use restriction reported that restricting formula during the birth hospitalization had no effect on breastfeeding duration.*[58] A cluster randomized trial found that the Ten Steps of the Baby Friendly Hospital Initiative[11] were effective at improving breastfeeding duration, but this study did not randomly assign formula restriction separately from the nine other interventions of the Ten Steps.[1] No previous studies have examined specific strategies for formula use and their effect on breastfeeding duration, according to a 2011 Cochrane systematic review.[57]

Natural History of Milk Production and Infant Weight Loss Suggests that Carefully Managed "Early Limited Formula" (ELF) May Benefit Many Mother-Newborn Pairs. Although low colostrum volume and associated newborn weight loss are physiological, they can potentially cause three interrelated problems for the breastfeeding dyad. First, low intake volumes and associated weight loss raise a newborn's risk of eventually meeting criteria for hyperbilirubinemia and dehydration, the most common morbidities of the newborn period.[59-64] Second, newborn weight loss with or without the development of associated morbidity may increase maternal anxiety and negatively impact other aspects of maternal experience, including breastfeeding self-efficacy and milk supply concern.[23, 25, 26, 65] Third, rapid weight loss in the beginning of the first week raises the risk of meeting criteria for excess weight loss later in the first week.[66] Excess weight loss, which typically develops around day 4-7, is usually defined as the loss of ≥10% birth weight and is usually treated with unrestricted volumes of formula fed to the point of infant satiation. This is important because once mature milk production begins, using formula to the point of infant satiation may have a detrimental impact on breastfeeding by causing breast milk stasis that activates the breast's Feedback Inhibition Loop (FIL) and reduces the volume of breast milk produced.[67, 68] Altogether, these three problems may lead to reduced breastfeeding duration, increased health care utilization and decreased maternal satisfaction with the quality of care. See Figure 1 for the potential effects of low early newborn intake.

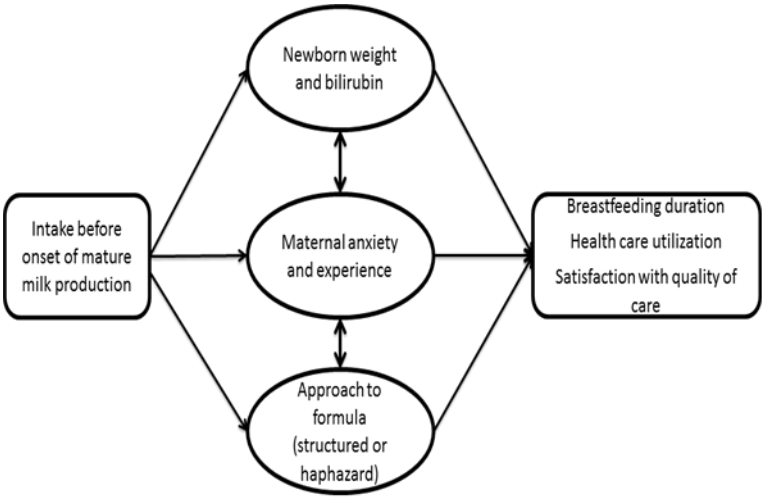


Figure 1: Potential effects of early newborn intake on shorter-term outcomes and subsequent outcomes

Our group's recent published analyses have reported that babies with rapid early weight loss are at greatly increased risk of this sequence of events, with an odds ratio of 3.30 (1.79, 6.07) for eventually developing excess weight loss.[29, 69] Since excess weight loss usually develops around days 4-7, such infants are at risk of receiving large volumes of formula *at or after* the onset of mature milk production, in a pattern that is likely to activate FIL and have a detrimental effect on breastfeeding. For such newborns, earlier use of limited volumes of formula, prior to the onset of mature milk production, might prevent excess weight loss and allow the discontinuation of formula at the onset of mature milk production. Such an approach to these particular infants, who we can now systematically identify, might avoid any activation of FIL and thus maintain the mother's milk supply.

Using small amounts of formula to supplement breastfeeding prior to copious maternal milk production could potentially ameliorate early newborn weight loss and reduce the need to use formula later in the first week. Since copious mature milk becomes available on average around 56 hours after birth,[21, 22] slightly later than mean age at discharge from U.S. birth hospitalizations,[70-72] if formula were to be used to ameliorate newborn weight loss and improve subsequent outcomes, the optimal time for beginning formula would likely be prior to the onset of mature milk production and therefore *prior* to hospital discharge. **Our group's recently published pilot data reported that random assignment to Early Limited Formula (ELF)—10 mL of**

formula after each breastfeeding prior to the onset of mature milk production—resulted in significantly *higher* rates of breastfeeding at 3 months than did the control assignment of standard of care, continued exclusive breastfeeding (95% vs. 68%, *p*=.04).

The carefully managed use of ELF prior to the onset of mature milk production could have effects on infants, mothers and the health care system. For babies with rapid early weight loss, using small volumes of formula before the availability of mature milk could provide nutrition and volume that might ameliorate weight loss, reduce the risk of morbidity associated with weight loss and reduce the need for large-volume formula supplement later in the first week. All these effects together might lead to improved duration of breastfeeding, so that babies can gain all the health benefits of breastfeeding. Since 21% of exclusively breastfeeding newborns have rapid early weight loss,[29] an effective strategy for early formula use for such infants could have substantial public health impact.

ELF might also reduce maternal anxiety. The postpartum period is a vulnerable time for maternal mental health; hormonal shifts combine with the profound lifestyle changes of motherhood to influence mood.[73] Low-income mothers are at even higher risk of mental-health problems.[74, 75] Rapid newborn weight loss can increase maternal anxiety and milk supply concern,[23, 25, 26, 28] which are associated with reduced breastfeeding duration.[27, 28, 76, 77] This team recently reported that mothers of newborns with excess weight loss were three times more likely to have a positive anxiety screen than mothers of newborns without excess weight loss.[23] The relationship between maternal anxiety attributable to newborn weight loss and other aspects of maternal experience such as breastfeeding self-efficacy, parenting self-efficacy, milk supply concern and postpartum depression has not previously been examined, but these aspects of maternal experience may be interrelated. Breastfeeding self-efficacy, milk supply concern, parenting self-efficacy and postpartum depression have each been correlated with both maternal anxiety and breastfeeding outcomes.[76, 78-86] If temporary early formula is effective at ameliorating newborn weight loss and thereby reduces maternal anxiety levels, it is possible that temporary early formula would have a synergistic effect that could improve breastfeeding self-efficacy, parenting self-efficacy and milk supply concern and potentially reduce postpartum depression.

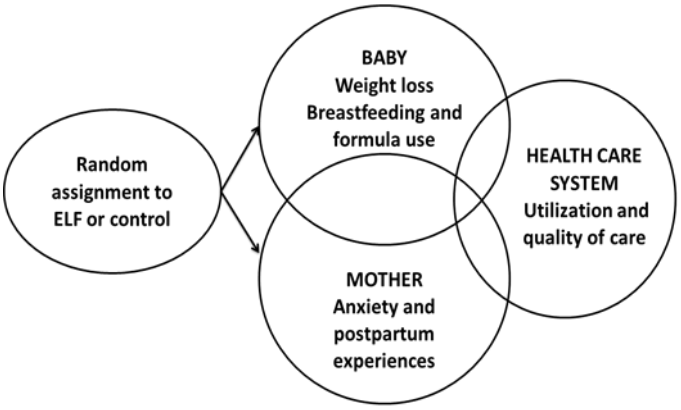


Figure 2: Effect of Feeding Approach on Baby, Mother and the Health Care System

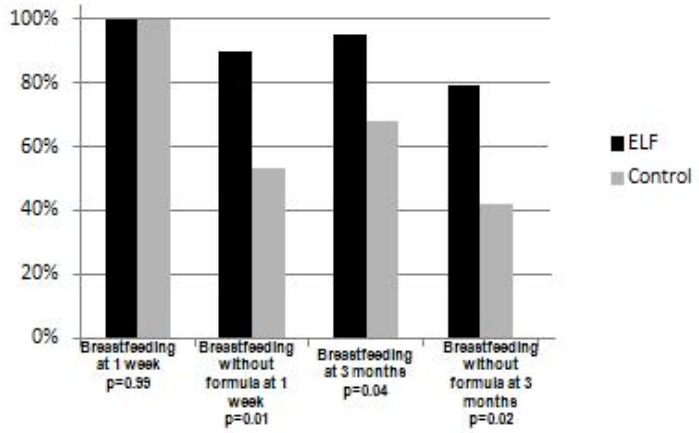
ELF might also have an effect on the health care system, potentially affecting health care utilization and maternal satisfaction with the quality of care. Excess weight loss increases a newborn's risk of rehospitalization and treatment for hyperbilirubinemia.[59, 62, 63, 87] Since quality of care is rated lower by the parents of children with poorer health status,[88] it is possible that newborn weight loss might also cause parents to rate lower the quality of care. The effect of ELF on the baby, mother and health care system will not be independent: ameliorating newborn weight loss might reduce maternal anxiety; lower maternal anxiety levels might lead to longer breastfeeding duration; and less weight loss and maternal anxiety might lead to lower health care utilization. (Figure 2)

The ELF strategy may appear counterintuitive in light of the observational evidence that early formula is associated with decreased breastfeeding duration and in light of current public health efforts aimed at reducing formula use during the birth hospitalization. However, it may be that a more nuanced approach to formula use, rather than an all-or-nothing strategy, could allow babies to obtain benefit from formula prior to mature milk production, discontinue formula at the onset of mature milk production and transition to sustained breastfeeding. Our ELF pilot results suggest that this is possible, but before any intervention using early limited volumes of formula can be recommended on a national scale, it will be critically important to demonstrate in a large-scale trial that early formula can be used in a way that supports breastfeeding.[89]

Supportive Pilot Data for the Innovative Intervention "Early Limited Formula" (ELF)

The ELF regimen is a well-defined protocol which incorporates four previously untested elements: (1) using a limited volume of 10 mL of formula after each breastfeeding; (2) beginning at 24-48 hours, (3) administering the formula with a syringe as opposed to a bottle with a nipple, (4) discontinuing formula at the onset of mature milk production and (5) using extensively hydrolyzed formula. Each ELF feeding uses 10 mL formula, much less than the 30-60 mL in a typical newborn formula feeding, in order to avoid satiating newborns and encourage frequent breastfeeds. ELF does not begin before 24 hours, giving mothers and babies a chance to experience exclusive breastfeeding. Since becoming accustomed to a rubber nipple may cause nipple confusion and interfere with proper latch at breast,[90] ELF uses a syringe to feed formula and does not use a bottle. Discontinuing formula once mature milk production begins may allow vigorous infant breastfeeding demand at that time, maximizing breast milk extraction and reducing feedback inhibition from milk stasis. In addition, the ELF technique uses extensively-hydrolyzed formula, which, while palatable to newborns, has a slightly unpleasant odor that may seem less desirable to parents. Extensively-hydrolyzed formula has the additional benefit of reduced risk of atopic and allergic disease when compared with cow's-milk-based and soy-based formulas.[91-93]

Figure 3: Results from the ELF pilot



Recently, our group conducted a pilot study of 40 exclusively breastfeeding newborns who had rapid early weight loss and randomly assigned these newborns either to ELF or to continued exclusive breastfeeding. Our results showed that those randomly assigned to ELF were more likely to be breastfeeding at 3 months than those randomly assigned to the control group of continued exclusive breastfeeding (95% vs. 68%, *p*=.04).[94] Additionally, we found that newborns in the ELF intervention group were much more likely to be breastfeeding without using any formula at 1 week than control newborns (90% vs. 53%; *p*=.01). ELF intervention infants remained more likely to be breast-feeding without formula than controls at 3 months (79% vs. 42%; *p*=.02). (Figure 3)

It is possible that using formula before the onset of mature milk production to reduce the use of formula at 1 week of age may be a powerful approach to supporting breastfeeding. Funded by Dr. Flaherman's Career Development Award from the NICHD (HD059818), our pilot offers a preliminary indication that ELF may help mothers meet Healthy People 2020 goals for breastfeeding at 6 and 12 months. The ELF protocol might also result in less overall volume of formula used through infancy. In this pilot, infants who were assigned to ELF used much less formula in the first month than infants who were assigned to the control group.

Tailoring Feeding Strategies to Best Pursue Healthy People 2020 Goals: Our work will be the first to explore whether feeding strategies can be tailored to the characteristics of the individual newborn. Although most exclusively breastfeeding newborns would obtain no benefit from formula, a subset meeting screening criteria may benefit from ELF. Our screening method for early identification of infants at risk for an extreme weight loss nadir demonstrates the strong relationship between rapid early weight loss (≥5% at <36 hours) and later excess weight loss (eventual loss ≥10%) described above.[95] Our group's most recent research suggests that weight loss ≥75th percentile may be an even stronger predictor of breastfeeding problems.[96] (Appendix II) By identifying infants at risk of such problems, we can be selective in providing ELF alternative feeding strategies, and as a result, we hope to help more newborns meet Healthy People goals for breastfeeding through 12 months.

A Potential Paradigm Shift in Newborn Care: Based upon strong preliminary data, the proposed study will offer direct, specific evidence of the effect of small amounts of formula followed by resumption of exclusive

breastfeeding on clinically relevant infant outcomes including breastfeeding duration and total formula use for those at-risk for unsafe neonatal weight loss. We will also examine the impact of our intervention on maternal experience including an assessment of the effect of ELF on maternal anxiety, breastfeeding self-efficacy, milk supply concern, parenting self-efficacy and depression and on health care system outcomes including health care utilization and maternal satisfaction with quality of care. In this way, we hope to provide a more comprehensive understanding of the potential health outcomes related to ELF.

Preliminary Studies:
Early Limited Formula Pilot. Dr. Flaherman was Principal Investigator for this pilot study[97] with the results described above. *The pilot data shows the potential beneficial effect of ELF on breastfeeding duration. This study also demonstrates our ability to work with a second enrollment site to recruit patients during the birth hospitalization, randomize to an intervention, and follow maternal and infant breastfeeding outcomes, as well as demonstrating our ability to teach a control intervention.*

Nurses for Infants Through Teaching and Assessment After the Nursery (NITTANY). Dr. Paul was principal investigator for the NITTANY trial (HRSA/MCHB R40MC 06630), which reported that among 1169 enrolled newborns, those randomly assigned to a nurse home visit were more likely to be breastfeeding at 2 weeks (92.3% compared to controls 88.6%, *p*=.04) and 2 months (72.1% compared to controls 66.4%, *p*=.05) but not 6 months. In this study, 55% of mothers were breastfeeding at 6 months.[98] NITTANY also found that high maternal anxiety scores are strongly associated with reduced breastfeeding duration.[27] *This study estimates breastfeeding rates at 6 months for the Penn State site and demonstrates the ability of our Penn State investigators to recruit mothers during the birth hospitalization, randomly assign them to an intervention and follow breastfeeding and anxiety outcomes.*

B. SPECIFIC AIMS

SPECIFIC AIM 1:

Establish that *early limited formula* improves breastfeeding duration and reduces formula use for newborns with rapid early weight loss ≥75th percentile. Early limited formula will be shown to **improve** breastfeeding duration and **reduce formula use for those enrolled** in a prospective trial based on data collected by the PI presented above under *Preliminary Studies*. A randomized, controlled trial will be conducted over a period of 36 months to demonstrate that early limited formula improves breastfeeding duration and reduces formula use. Secondary outcomes of importance will include maternal experiences including volume of formula used and breastfeeding duration and formula use at 1 week and 1, 3, 6 and 12 months. In secondary analysis, we will also report the relationship between ELF and breastfeeding duration by percentile zone of weight loss (≥95th, ≥90th, and 75th percentiles).

SPECIFIC AIM 2:

Establish that *early limited formula* reduces maternal anxiety. Maternal anxiety is highly correlated with perception of insufficient milk supply and with newborn weight loss, and all these together greatly increase a dyad's risk of breastfeeding discontinuation. It is possible that the temporary use of early limited formula will ameliorate maternal anxiety and allow sustained breastfeeding. In this aim, we will also explore whether ELF is effective at modifying other aspects of maternal experience such as breastfeeding self-efficacy, parenting self-efficacy, milk supply concern and postpartum depression.

SPECIFIC AIM 3:

Prospectively evaluate the effect of early limited formula on the healthcare system. Low enteral intake and corresponding newborn weight loss are highly correlated with the two most common causes of healthcare utilization after the birth hospitalization: jaundice and dehydration. It is possible that increasing enteral intake and ameliorating weight loss may reduce the incidence of jaundice and dehydration, potentially leading to fewer outpatient visits, fewer emergency room visits and fewer hospital readmissions. We will also measure the effect of ELF on maternal satisfaction with the quality of care.

EXPLORATORY AIM:

Prospectively evaluate the effect of early limited formula on the infant intestinal microbiome. We will collect and store infant stool specimens at 1 week and 1 month of age. Specimens will be stored at the University of California Davis for future analysis of the effect of ELF on the intestinal microbiome.

III. PROTOCOL

In the ELF-TLC study, the effectiveness of ELF will be evaluated prospectively and compared with standard of care, which is continued exclusive breastfeeding, using a randomized, controlled study design. We will attempt to improve breastfeeding duration and reduce morbidity in the neonatal/postpartum period using small volumes of formula after each breastfeeding, discontinued at the onset of mature milk production. Although previous studies have shown that early formula use is associated with decreased breastfeeding duration, ELF incorporates five previously untested elements that may allow ELF to improve infant nutrition and hydration without interfering with the natural breastfeeding process. These elements are: (1) ELF uses a limited volume of formula, only 10 mL of formula after each breastfeeding. This volume is much less than the 30-60 mL in a typical newborn formula feeding, and thus may avoid satiating newborns and encourage frequent breastfeeds; (2) ELF begins at 18-72 hours, after mother and baby have had some time for exclusive breastfeeding; (3) ELF formula is fed with a syringe as opposed to a bottle with a nipple, which may reduce nipple confusion and allow good latch at breast (4) All ELF formula is discontinued at the onset of mature milk production. Discontinuing formula once mature milk production begins may allow vigorous infant breastfeeding demand at that time, maximizing breast milk extraction and reducing feedback inhibition from milk stasis; and (5) using extensively hydrolyzed formula, which, while palatable to newborns, has a slightly unpleasant odor that may seem less desirable to parents.

Over an 18-month period we will prospectively enroll a cohort of 164 healthy, term singleton newborns and their mothers admitted to the hospital nursery who are exclusively breastfeeding and have weight loss of ≥75th percentile for age based on an hourly nomogram demonstrating percentiles of newborn weight loss generated from a large sample of exclusively breastfed newborns.(ref) Previous data have indicated that newborns with this level of weight loss are at greatly increased risk of eventually losing 10% or more of their birth weight and therefore requiring supplementation with large volumes of formula, sometimes known as “rescue formula use”. In this study, patients will be randomized to receive either early limited formula or to continue breastfeeding exclusively unless otherwise instructed by a health care provider. For each newborn and mother, information from the pregnancy, obstetrical record, and the nursery course will be collected. Data also will be recorded regarding duration of breastfeeding, compliance with and extent of early limited formula use, maternal anxiety, newborn readmissions, ED visits, outpatient visits and maternal satisfaction with care. Maternal breastfeeding self-efficacy, parenting self-efficacy, milk supply concern and postpartum depression will also be assessed.

A. STUDY GROUPS AND SUBJECTS

Of the approximately 2000 newborns born at UCSF each year and 1800 newborns born at Hershey Medical Center each year, we estimate that about 40% will meet study entry criteria of breastfeeding exclusivity and weight loss ≥75th percentile before 48 hours of age. Therefore, over an 18-month recruitment period, of 2000 newborns admitted to the nursery at UCSF and 1800 newborns admitted to the nursery at Hershey, approximately 1520 mother/baby pairs will be eligible for enrollment (800 at UCSF and 720 at Hershey). Our enrollment targets are 84 mother-baby pairs for UCSF and 80 mother-baby pairs for Hershey. At randomized assignment, pairs will be stratified by site (UCSF or Hershey), income (<200% Federal Poverty Level (FPL) or ≥200% FPL) and parity (primiparous or multiparous). About 32% of mothers are estimated to have household incomes <200% of the FPL. About 50% of mothers of eligible babies are expected to be primiparous.

Covariates will include maternal demographic factors such as ethnicity/race, age, marital status, education, and insurance type. Also, we will collect data on maternal clinical features such as previous breastfeeding experience, birth outside of the U.S., education, income, language preference, prior participation

in a breastfeeding class, previous breast surgery, pre-pregnancy body mass index, intended duration of any and exclusive breastfeeding, multiple birth, importance attributed to breastfeeding, planned time of return to employment and whether or not the mother saw a lactation consultant while in the hospital and data on infant factors including gestational age, birth weight, weight loss at enrollment and latch score.

B. INCLUSION CRITERIA

Based on sample size calculations, we will enroll 164 mother/infant pairs meeting these inclusion criteria:

1) Full term, healthy singleton infant (≥ 37 0/7 weeks gestational age) in well newborn nursery
2) Exclusively breastfeeding (has not received any feedings other than breast milk)
3) Infant is 18-72 hours old
4) Infant has weight loss of ≥75th percentile on delivery mode specific nomogram (Appendices IIa, IIb; available at www.newbornweight.org) documented at 12-72 hours of age
5) English-speaking mother

C. EXCLUSION CRITERIA

1) Mothers or infants for whom breastfeeding is not recommended by the clinical team
2) Mothers who have already begun to produce mature breast milk[99]
3) Any formula or water feeding prior to enrollment
4) Infants who have already lost ≥10% of their birth weight
5) Family with no active telephone number (home or cellular)
6) Plan for infant adoption or foster care
7) Mothers <18 years of age
8) Infant receiving scoring for Narcotic Abstinence Sydrome

D. RATIONALE FOR INCLUDING THOSE WHO HAVE LOST ≥75th PERCENTILE OF BIRTH WEIGHT

Weight loss of ≥75th percentile is by definition not unusual and will occur in 25% of babies. The proportion experiencing this level of weight loss is likely higher in academic medical centers such as UCSF and HMC, where mothers are more likely to have pre-existing conditions that may interfere with optimal breastfeeding. However, although such weight loss can be normal for healthy term infants, it may predict an increased risk of eventual weight loss of 10% or more of birth weight.[100] Infants with 10% weight loss are at much greater risk of hypernatremic dehydration, and for this reason treatment with ad lib volumes of formula is usually begun if an infant has lost 10% or more of their birth weight.

This is important, because ad lib formula administration at the time of 10% weight loss, which usually occurs around day 3-5 after birth, may have important negative consequences. Ad lib formula administration may interfere with a baby's interest in breastfeeding, and extensive formula use at 3-5 days of age may coincide with the onset of mature maternal milk production. Since vigorous infant suckling is necessary at the onset of mature milk production to sustain a strong maternal milk supply, ad lib formula administration at 3-5 days of age can be very damaging to sustained breastfeeding. Since early weight loss of ≥75th percentile may predict increased risk of eventual weight loss of ≥10%, early weight loss of ≥75th percentile may therefore also predict a greatly increased risk of ad lib formula administration at 3-5 days of age. The use of ELF might preclude the development of 10% weight loss, allow unconstrained exclusive breastfeeding at the onset of mature milk production and therefore reduce the likelihood that sustained breastfeeding will be damaged by ad lib formula begun at 3-5 days.

E. RATIONALE FOR EXCLUDING THOSE WHO HAVE RECEIVED FORMULA OR WATER

Exclusive breastfeeding without any supplementary formula or water is recommended by multiple public health organizations and is standard of care for healthy term newborns. This study is designed to compare such exclusive breastfeeding to the carefully managed formula of ELF, so therefore we will not enroll infants who are not exclusively breastfeeding. Oral medications are not excluded from WHO and CDC definitions of exclusive breastfeeding, so any babies who have received Sweetease or other similar for analgesia can still be included in this study.

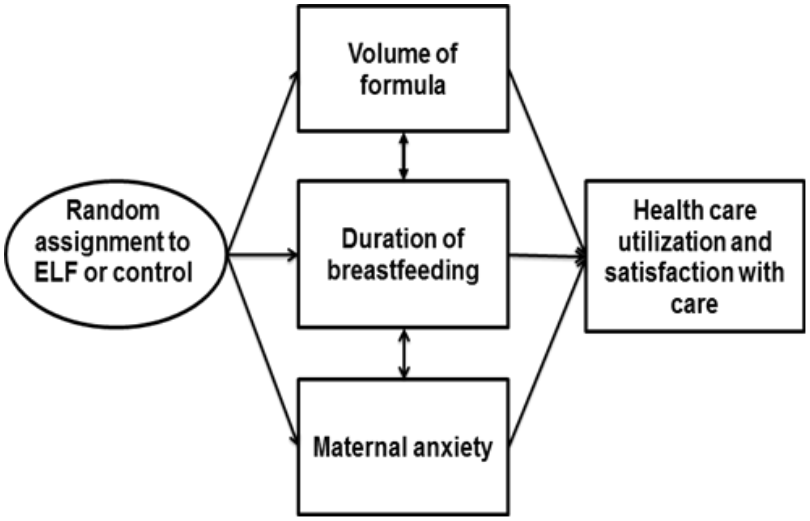
F. OUTCOME MEASURES AND THE RATIONALE FOR CHOOSING THEM

The primary outcome in this investigation will be the duration of breastfeeding, which will be assessed at 1 week and at 1, 3, 6 and 12 months. If this intervention is successful at improving rates of breastfeeding at 6 months of age, we may be able to provide evidence to support changes in practice that will allow more mothers and babies to reach the Healthy People 2020 goals of breastfeeding through 6 months and through 12 months. Another important outcome in this study will be formula use, and we will be assessing both any use of formula at 1 week and 1, 3, 6 and 12 months of age and the total volume of formula used. If the use of small volumes of formula in the period prior to the onset of mature milk production is successful at improving breastfeeding rates at 1, 3, 6 and 12 months of age, the overall volume of formula used for each baby randomly assigned to ELF will be very much lower than the overall volume of formula used for each control who discontinued breastfeeding prior to 1, 3, 6 or 12 months of age.

The immediate postpartum period is a time of high state anxiety levels for mothers, and we will assess how ELF affects maternal state anxiety by using the State Trait Anxiety Inventory (STAI). It may be that using small volumes of formula after each breastfeeding prior to the onset of mature milk production may reduce maternal anxiety about breastfeeding, potentially leading to improved overall maternal mental health. In order to further assess the potential impact of ELF on maternal mental health, we will also examine the outcome of postpartum depression using the Edinburgh Postnatal Depression Survey (EPDS). Measuring this important outcome will also allow us to identify any mothers who need additional supportive services and refer them to care during this vulnerable period (see Section IV.E.). We will also assess the effect of ELF on maternal breastfeeding self-efficacy and maternal milk supply concern, because both of these are important predictors of breastfeeding duration. Additionally, we will examine the effect of ELF on healthcare utilization including office visits, ER visits and hospital readmission. We acknowledge that clinicians have varying thresholds for readmission and follow-up, but believe this study will allow for a “real world” evaluation of readmission since guidelines for management of conditions such as hyperbilirubinemia are not universally followed. As such, data will be collected on the reasons for hospitalization, office visits and ER visits, including bilirubin levels when jaundice is the cause for a readmission.

Because the first few days after the birth is a critical period for the successful establishment of breastfeeding, we anticipate that early intervention with ELF might potentially affect breastfeeding rates throughout the first year. For this reason, we will follow outcomes related to breastfeeding duration for 12 months. Since we anticipate that the potential effect of ELF on maternal anxiety and healthcare utilization are unlikely to extend beyond 1 month, we will follow these secondary outcomes at 1 week and 1 month. See Table 4 for a summary of study outcome assessment. The potential relationships between the intervention and the assessed health outcomes are displayed in Figure 4.

Fig 4. Relationship between ELF and maternal, infant and health systems outcomes



G. STUDY CONTACT WITH PARTICIPANTS

This study will have only one in-person visit, occuring at the time of enrollment with the study RN. At that time, baseline information will be collected, the study RN will teach either the intervention or the control, and brief outcomes related to the intervention or control will be collected. Subsequently, there will be 5 followup calls at: 1 week, 1 month, 3 months, 6 months and 12 months.

1) Visit (24-48 HOURS) – Newborn Nursery

a) Newborn and Maternal chart review in newborn nursery/maternity floor to determine eligibility based on inclusion and exclusion criteria
b) Obtain informed consent
c) Complete enrollment data collection forms (Item C can be deferred until after Item K if mother is currently ready to breastfeed)
   - INFANT: record birth weight, gestational age and weight loss at enrollment
   - MOTHER: record age, parity, race/ethnicity, method of delivery, previous breastfeeding experience, birth outside of the U.S., education, income, language preference, prior participation in a breastfeeding class, previous breast surgery, pre-pregnancy body mass index, intended duration of any and exclusive breastfeeding, multiple birth, importance attributed to breastfeeding, planned time of return to employment and inpatient access to a lactation consultant. Record additional data on lactation including: time of first breastfeeding, number of breastfeedings in the first 24 hours, planned method of feeding, planned length of breastfeeding, whether mother is having breastfeeding problems now, what problem mother is having, whether or not mother is pumping, hand expressing or using a nipple shield. For mothers who have previous breastfeeding experience, whether they had a problem and what it was.
d) Ascertain when mother is next planning to breastfeed her infant and tell mother study nurse will return at that time. Exchange contact information so that mother can notify study nurse if feeding occurs earlier than planned.
e) Return at the time of the next breastfeeding.
f) Support mother in breastfeeding her infant and provide breastfeeding education. Mother should attempt both breasts unless she wishes to use only one. Provide breastfeeding education to all mothers on the following topics while supporting and advising breastfeeding: hunger cues, hand expression, positioning, latch and breastfeeding duration. Encourage all mothers to breastfeed 8-12 times/day at least until weight gain is established. Review normal patterns of voiding, stooling, weight loss and milk production. Detailed description of breastfeeding education is in Table 1 below. In the event that the newborn is unable latch after 15 minutes of attempt, move ahead to Item G after 15 minutes. Total breastfeeding teaching time on average is estimated to require about 30 minutes.
g) Distribute handout summarizing this teaching. (Appendix 1)
h) Record LATCH score, approximate volume expressed during hand expression and positions taught.
i) Randomize subject to treatment groups
j) Based on randomization arm, teach EITHER intervention (Table 2) or control (Table 3) as detailed below.

Table 1: Breastfeeding education for both groups in the ELF Study
Hunger cues: Newborns can give a variety of hunger cues. Mothers should try to breastfeed as soon as early hunger cues occur, such as when babies turn their heads back and forth, open their mouths, move their mouths from side to side (rooting), or suck their hands or thumbs. Waiting for later hunger cues such as crying can make it more difficult to obtain a good latch.
Hand expression: Teach using the press/compress/release method described by Jane Morton at the web site http://newborns.stanford.edu/Breastfeeding/HandExpression.html. This website should also be recommended to parents for future viewing.
Positioning: Teach cradle, cross-cradle or football as desired by mother. If the mother's physical condition allows it, teach an alternate position on the second breast.
Latch: Show mother how to wait for baby's mouth to open wide. Bring baby towards breast, not breast toward baby. Baby should engulf as much of the areola as possible in a manner with a bit more areola in the direction of the baby's chin. Once latched, there should be 180° angle where the baby's upper lip meets the lower lip. If

initial latch is suboptimal, re-attempt after showing mother how to break suction by inserting her 5th digit in the corner of the baby's mouth. Alternatively, or in addition to breaking the latch, study nurse may teach mother how to pull baby's chin down once latched to improve latch.
Duration: Baby should breastfeed 10-20 minutes from each breast. Teach mother that babies naturally pause often during early breastfeeding, and should suck approximately 50% of the time that they are latched. If baby is not sucking 50% of the time, can stimulate baby by rubbing back or soles of feet, or blowing on baby's head. Do not rub baby's cheek when latching, this can generate rooting towards cheek which can interfere with latching. If baby still does not suck 50% of the time and breastfeeding has been less than 10 minutes on a breast, remove baby from breast, remove clothes and blankets and let baby lie in crib for a minute until he wakes up, then attempt breastfeeding again to complete at least 10 min per breast of attempted breastfeeding. After 20 minutes, mother should remove baby from breast.
Frequency: Educate mothers to breastfeed 8-12 times per day, approximately every 2-3 hours at least until weight gain is established. Teach mothers that cluster feedings are normal, where baby may breastfeed every hour for a few hours, and then sleep for a few hours. However, mothers should not let babies breastfeed for more than 40 minutes at a time. After 40 minutes of breastfeeding, mothers should take a break for at least 20 minutes or so to allow recovery of both mother and baby. During the day, it's best not to have baby sleep more than 2-3 hours without a feeding. If baby is breastfeeding 8-12 total in 24 hours, it's okay to go as long as 5 hours at night without breastfeeding at one time during the 24-hour period. During the first 2 weeks after delivery, if more than 5 hours elapse at night without breastfeeding, mothers should wake babies and feed.
Voiding: Babies should void at least once per day of age, so that a 3-day-old baby should void at least three times on the third day, a 4-day-old baby should void at least four times on the fourth day, etc. By 7 days of age, babies should be voiding 8-12 times per day. Urine that is the color of brick dust is normal during the first week after birth because many babies are not fully hydrated.
Stooling: Babies should stool at least once per day of age, so that a 3-day-old baby should stool at least once on the third day, a 4-day-old baby should stool at least twice on the fourth day, etc. By 7 days of age, babies should be stooling 8 times per day. Stool will be initially black (meconium), and then transition to yellow/mustard color when mature milk is in.
Weight loss: All breastfed newborns lose weight daily for the first few days after birth. Babies are born with extra fluid and weight loss is normal and universal. Frequent breastfeeding will encourage weight gain.
Milk production: Mothers do not produce mature milk until 2-5 days after birth, or 2-7 days for primiparous mothers. Before mature milk production, mothers produce an early milk called colostrum that is high in protein and antibodies. Colostrum can be clear, yellow or even orange. Colostrum helps establish the healthy bowels associated with breastfeeding, and it benefits babies to swallow as much colostrum as possible.

Table 2: Early Limited Formula Teaching (Intervention Group)
Formula preparation: Wash hands. Gently agitate the bottle of extensively hydrolyzed formula, Enfamil® Nutramigen®. Select a new feeding syringe. Open formula bottle. Insert feeding syringe and remove 10 mL of formula. (*While in hospital:* mother should discard remaining formula. *When home,* mother should refrigerate remaining formula for later use. Previously refrigerated formula should be drawn up in a new syringe and then held under warm running water for a few minute to bring it to room temperature.)
The following steps should be first performed by the study nurse, using about 5 mL of the formula. After about 5 mL have been ingested, all of the following steps should be repeated by at least one parent.
Position baby: Baby should be comfortably reclining with head slightly higher than body. Baby can be propped on mother or father's legs, or held in cradle position by one parent and fed ELF by other parent, or can sit in car seat if available.
Initiating sucking reflex: Wash hands again. Nurse should put on gloves, parents feed without gloves. Place appropriately-sized finger, palmar side up, in baby's mouth. Mothers often use the index finger; fathers often use the pinky finger. Soft part of finger should make contact with baby's hard palate, and sucking reflex will be activated. (Note: if baby sucks only a little bit and then falls asleep, check placement of finger and proceed to next step). Leave finger in place for next step.
Feeding: Without moving sucking finger, place tip of syringe in the corner of baby's mouth. Depress feeding syringe slightly to release about 0.3 mL of formula into mouth. That means, for each mL of formula ingested, syringe will be depressed about 3 times. Babies drink only a small amount of formula at any given time, and it

will take about 30 swallows for baby to ingest all formula. After depressing syringe and releasing about 0.3 mL of formula, wait for baby to swallow and then wait for the next suck. Once the next suck occurs, depress syringe and release formula again. The sequence may occur quite rapidly at the very beginning of feeding, and then may become slower as feeding progresses. If baby is feeding rapidly at beginning, try to keep up with demand by depressing syringe slightly after each swallow/suck cycle. If baby is not feeding rapidly, carefully wait until formula is swallowed and the next suck occurs before depressing syringe.
Leaking: Some formula may leak from side of mouth, please wipe as this occurs.

Table 3: Safety Teaching (Control Group)[101]
Car seat safety: Baby should always be placed in rear-facing car seat in the back seat of the car. Baby must remain in seat throughout travel. Straps in the car seat should be adjusted to fit snugly around baby, following manufacturer's instructions. Car seat must be firmly and correctly affixed to car. You can find a location to check the position of your car seat on http://www.safercar.gov/cpsApp/cps/index.htm. Discuss common situations in which correct car seat use may be difficult and troubleshoot how parents might address these (e.g. baby is crying when car is on highway—find a safe place to pull over and comfort baby; using a taxi, take the time to install the seat properly; etc.)
Parent car safety: Always wear your seat belt. This helps maintain better control of the car in case of an accident. Do not drive under the influence of alcohol or drugs. Many postpartum medications can make mothers sleepy, and new mothers may also be very sleepy even without medications. Do not drive with your baby if you have any concerns about alertness. Avoid distracted driving and never handle your cell phone while driving.
Smoking: Even occasional exposure to cigarette smoke can damage babies' lungs, and smoke exposure is highly correlated with Sudden Infant Death Syndrome (SIDS). Keep your home and vehicle smoke-free, and do not allow anyone to smoke in your home or vehicle. If you or someone living in your house smokes, it's important to quit now. Even if you only smoke outside, smoke can cling to your hair and skin and your baby can be exposed.
Falls: Keep one hand on your baby at all times while changing diapers and clothes. Babies can move and even start to roll, and injuries can occur unexpectedly, so vigilance about falls is necessary.
Home: Install smoke detectors and carbon monoxide detectors and carefully follow instructions on timing of when to change batteries. Set home water temperature to <120°F. Avoid drinking hot liquids while holding baby. Never place hot liquids next to baby on changing table or in crib.
Sleep: Place baby to sleep on back in crib with slats ≤2 3/8" apart. No pillows, bumpers, stuffed animals or fluffy bedding in crib. The safest place for baby to sleep is in a crib, cradle, co-sleeper, or bassinet next to your bed. Babies should never sleep in the parents' bed if there has been any use of drugs or alcohol.

Phone follow-up assignments: The first two participants randomly assigned to ELF each month will receive 1-week phone follow-up from the Penn State team, who will enter the responses directly into RedCAP. All other phone follow-up calls will be made by the UCSF team.

2) <u>Follow-up call (8 days of age) – Telephone Call</u>

a) Breastfeeding
- Breastfeeding status (yes/no)
- Reasons for discontinuing breastfeeding (if applicable)
- Formula use in last 24 hours (yes/no)
- Volume of formula used
- Any other feedings
- Day and time at onset of mature milk production

For the first two participants randomly assigned to ELF each month, we will also ask questions about:
- ELF use on day of enrollment
- ELF use on subsequent days

b) Breastfeeding Self-Efficacy Scale—Short Form[84]
c) Infant Satisfaction and Satiety Scale[102]
d) Parenting Sense of Competence Scale[103]

e) State Trait Anxiety Inventory (STAI)[104] - State Portion only –if score ≥40, refer to Primary Care Provider (PCP) if mother has one, obstetrical service if no PCP.
f) Edinburgh Postnatal Depression Scale (EPSD)[105] - If score ≥12, refer to PCP if mother has one, obstetrical service if no PCP. If Penn State team has made the follow-up call and identified an EPDS ≥12, the Penn State team member will call Dr. Flaherman to report.
g) Outpatient visits, emergency room visits, inpatient hospitalizations and their associated reasons/diagnoses, with weights and bilirubin levels if available

3) **Follow-up call (1 month of age) – Telephone Call**
All items completed on paper forms by interviewer contemporaneously with interview
a) Breastfeeding
- Breastfeeding status (yes/no)
- Reasons for discontinuing breastfeeding (if applicable)
- Formula use in last 7 days (yes/no)
- Volume of formula used in a typical feeding in the last 7 days
- Typical frequency of formula feedings in the last 7 days
- Any other feedings

b) Breastfeeding Self-Efficacy Scale—Short Form
c) Infant Satisfaction and Satiety Scale
d) STAI - State Portion only –if score ≥40, refer to PCP if mother has one, obstetrical service if no PCP.
e) EPSD - If score ≥ 12, If score ≥ 12, refer to PCP if mother has one, obstetrical service if no PCP.
f) Outpatient visits, emergency room visits, inpatient hospitalizations and their associated reasons/diagnoses, with weights and bilirubin levels if available

4) Follow-up call (3 months of age) – Telephone Call
All items completed on paper forms by interviewer contemporaneously with interview
a) Breastfeeding
- Breastfeeding status (yes/no)
- Reasons for discontinuing breastfeeding (if applicable)
- Formula use in last 7 days (yes/no)
- Volume of formula used in a typical feeding in the last 7 days
- Typical frequency of formula feedings in the last 7 days
- Any other feedings

b) Breastfeeding Self-Efficacy Scale—Short Form
c) Infant Satisfaction and Satiety Scale

5) Follow-up call (6 months of age) – Telephone Call
All items completed on paper forms by interviewer contemporaneously with interview
a) Breastfeeding
- Breastfeeding status (yes/no)
- Reasons for discontinuing breastfeeding (if applicable)
- Formula use in last 7 days (yes/no)
- Volume of formula used in a typical feeding in the last 7 days
- Typical frequency of formula feedings in the last 7 days
- Any other feedings

b) Breastfeeding Self-Efficacy Scale—Short Form
c) Infant Satisfaction and Satiety Scale

6) **Follow-up call (12 months of age) – Telephone Call**
All items completed on paper forms by interviewer contemporaneously with interview
a) Breastfeeding
- Breastfeeding status (yes/no)
- Reasons for discontinuing breastfeeding (if applicable)

Table 4. Summary of study outcome assessment

Outcome	Measurement tool	Time of assessment					
		Baseline	1 wk	1 mo	3 mo	6 mo	12mo
Aim 1—Infant							
Clinical and demographic screening information	ELF-TLC instrument	X					
Any breastfeeding	National Immunization Survey (NIS)[106] breastfeeding items		X	X	X	X	X
Type of feeding other than breast milk, if any	Infant Feeding Practices Study (IFPS) breastfeeding items[107]		X	X	X	X	
Formula volume used	IFPS breastfeeding items[107]		X	X	X	X	
Latching	LATCH score	X					
Aim 2—Mother							
Anxiety	State Anxiety Scale of the State-Trait Anxiety Inventory[104]	X	X	X			
Breastfeeding self-efficacy	Breastfeeding Self-Efficacy Scale—Short Form[84]	X	X				
Milk supply concern	Infant Satisfaction and Satiety subscale of H&H Lactation Scale[102]	X	X				
Postpartum depression	Edinburgh Postnatal Depression Survey[105]	X	X	X			
Aim 3—Health care system							
Health care utilization	Maternal report of office visit, emergency visit, re-hospitalization		X	X			
Maternal satisfaction with quality of care	Satisfaction with Health Care Following Childbirth Scale[108]		X				

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IV. PROTOCOL IMPLEMENTATION

A. RECRUITMENT

During the maternity and newborn hospital stay at UCSF and HMC, study personnel will identify eligible mothers and babies through a review of the electronic medical record. Once dyads are identified as meeting each of the inclusion criteria, informed consent will be obtained from the mother.

B. PARTICIPANT RETENTION

It is expected that dropouts may occur over the course of the 12-month follow-up period. The vast majority of those dropouts are unlikely to occur in the first month of the study, but by the 6-month outcome assessment a 10% dropout rate was included in sample size calculations. To minimize drop-outs, we will obtain multiple phone numbers for each participant and will obtain the phone number of at least one contact who does not live with the participant. We will have a dedicated call-back number and use multiple reminder calls to obtain robust follow-up. To further protect against loss to follow-up for breastfeeding duration, we will obtain permission at enrollment to request medical records for babies with missing data to gain information on breastfeeding duration and formula use.

C. STUDY NURSE TRAINING

The nurses responsible for teaching the intervention or control will be research nurses with experience in breastfeeding teaching. Prior to the start of this study, all nurses will receive education on the support of breastfeeding mothers and in particular on the teaching of ELF and safety education. The PI Dr. Flaherman is board certified as both a pediatrician and a lactation consultant and will lead this educational initiative. All nurses as well as study staff have received training on cultural competency.

D. HEALTHCARE UTILIZATION ASSESSMENT

Maternal and infant healthcare utilization will be primarily assessed via maternal report using a healthcare utilization survey. Though maternal report has been shown to be a reliable indicator of actual healthcare utilization,[109] a subset of mother/infant dyads that receive all care at either UCSF or HMC and their affiliated clinics will have their utilization objectively assessed using the hospital scheduling and/or billing databases. The concordance between self-report and documented visits will be determined for this subset. In case the concordance is not sufficient, included in the informed consent will be permission to access the outpatient medical record including clinics outside of the HMC system.

E. MICROBIOME

Infant stool will be collected at 1 week and 1 month from infants enrolled at UCSF and will be stored by investigators at UC Davis for future analysis of the effect of our intervention on infant microbiota.

E. RISKS/BENEFITS

Risks to the subjects.

Human subjects involvement and characteristics. This study will involved a total of 164 healthy term newborns and their mothers who are patients at UCSF Medical Center and the Penn State Milton S. Hershey Medical Center. We will include newborns 18-72 hours old who have weight loss ≥75th percentile based on the weight loss nomogram stratified for delivery mode since this criterion may predict increased risk of breastfeeding problems. We will exclude those requiring Level II or Level III care, newborns whose mothers have conditions that are contraindications to breastfeeding (e.g. HIV, active TB, receipt of chemotherapy) and those who have lost ≥10% birth weight. All eligible mother-infant pairs will be approached for potential recruitment and enrollment. Since this study will examine the effect of a breastfeeding intervention in the newborn period, our study participants will be neonates. Participants will be randomly assigned to either the intervention or the control group. The intervention group will receive 10 mL of formula in addition to breastfeeding, while the control group will breastfeed exclusively unless otherwise directed by a health care provider. UCSF is the primary site and plans to enroll 84 newborns; Penn State plans to enroll 80 newborns. Data from both sites will be entered directly onto the password-protected server of UCSF's Research Encrypted Data Capture (REDCap). Protected Health Information (PHI) will be removed from the data before it is exported to the UCSF Principal Investigator, Valerie Flaherman, MD, MPH, for analysis.

Sources of materials. The research material will consist of survey responses and medical history reports. Dr. Flaherman, PI, Dr. Cabana (co-investigator) and Dr. Paul (site PI for Penn State) will have access to protected health information, as will the project managers and research nurses from the two sites and the research assistant at UCSF. All identifiable private information will be maintained on a password-protected server maintained by UCSF's REDCap.

Potential risks. Since both exclusive breastfeeding and mixed feeding with formula and breast are common in the newborn period, we do not anticipate any additional medical risks to the patients that exceed the usual risks surrounding the postpartum period for newborns. However, loss of privacy may be a risk, as we will collect some information individuals might prefer to keep private, such as income, education, previous breastfeeding experience and parenting self-efficacy. Eligible participants who do not want to enroll in the study will receive usual care, and may choose to breastfeed exclusively, to breastfeed with some formula use or to stop breastfeeding.

Protection Against Risk: To protect against the risk of loss of privacy, all potential participants will be approached in their private hospital room, which house all mothers at both study sites. Study investigators will also consent, enroll and teach the intervention in the participant's private hospital room. To protect against a

loss of confidentiality of data, all data will be entered into UCSF's RedCAP, a research database server with password-protection maintained by UCSF. All paper records, including signed informed consent, will be kept in either a locked filing cabinet in Dr. Flaherman's locked office at UCSF, or a locked filing cabinet in the locked office of the project manager at Penn State. The study investigator will obtain informed consent from mothers for themselves and their newborns. Improving outcomes for newborns is the main outcome of this study and therefore it is necessary to enroll neonates in this study. See below for Data Safety and Monitoring Plan.

Potential benefits of the proposed research to the subjects and others. All study participants will receive breastfeeding support at enrollment, which will supplement and not replace breastfeeding support available during the course of their usual clinical care. In addition, parents of participants may have the benefit of knowing that they are helping contribute to a greater understanding of the impact of early infant feeding on subsequent health outcomes. The study risks of loss of privacy and loss of confidentiality may therefore be balanced by the potential benefit of breastfeeding support and the potential feeling of satisfaction from helping contribute to knowledge of the impact of early feeding.

The maternal mental health outcomes of anxiety and depression will be assessed in this study at 1 week and 1 month using the State Trait Anxiety Inventory (STAI) and the Edinburg Postpartum Depression Scale (EPDS). In order to insure adequate protection of mothers from the risk of adverse mental health outcomes, STAI and EPDS total scores will be calculated within 24 hours of maternal interview. Mothers with positive screening tests on either the STAI (STAI score ≥40) or the EPDS (EPDS score ≥12) will be referred to their primary care provider immediately for further evaluation. If no primary care provider has been identified for an individual mother, she will be referred to her obstetrician for further evaluation. The study risks of loss of privacy and loss of confidentiality may therefore be balanced by the increased surveillance and referral for anxiety and depression, in addition to the potential benefit of breastfeeding support and the potential feeling of satisfaction from helping contribute to knowledge of the impact of early infant feeding.

Importance of the knowledge to be gained. Breastfeeding for at least 12 months reduces infectious disease in infancy and reduces maternal risk of breast and ovarian cancer, but most mothers and infants stop breastfeeding in the first few months after birth. In this proposed study, we aim to examine whether a specific feeding strategy might improve breastfeeding duration. Since the risks to privacy and confidentiality are relatively small for participants in this study, the risks to participants are reasonable in relation to the importance of the knowledge to be gained.

F. ANTICIPATED RESULTS

If our randomized trial shows that ELF improves breastfeeding duration, it might be possible to use ELF to help meet Healthy People 2020 targets for breastfeeding at 6 and 12 months and allow more mothers and babies to obtain all the benefits of continued breastfeeding. Our results could also potentially inform the modification of breastfeeding guidelines from the WHO,[11] the CDC,[13] the AAP[110] and the Joint Commission,[41-43] so that the use of formula could be tailored to the needs of individual infants based on their individual clinical presentation. In addition to improving U.S. breastfeeding rates, such a tailored strategy might also ameliorate maternal anxiety and reduce health care utilization, potentially leading to improvement in maternal satisfaction with the quality of health care.

If the use of this intervention helps breastfeeding rates meet Healthy People 2020 targets, this project could have a substantial impact on population health by reducing rates of infectious disease during infancy and by decreasing future rates of maternal breast and ovarian cancer.

V. ADVERSE EVENTS

A. DEFINITIONS

An adverse event shall be defined as any detrimental change in the patient's condition, whether it is related to perinatal care or to another unrelated illness.

B. ADVERSE EVENTS

Adverse events may be grounds for withdrawal from the study if the patient is no longer able to effectively participate in the study. Subjects experiencing minor illnesses that are considered part of normal childhood such as acute otitis media, upper respiratory infections, and gastroenteritis not resulting in a hospitalization will not be recorded as adverse events. Adverse events that will be recorded include jaundice/hyperbilirubinemia requiring phototherapy, intravenous fluid administration, and laboratory evaluations of any kind not related to a prenatal diagnosis (e.g. renal ultrasound to follow up on antenatal hydronephrosis, hip ultrasound due to intrauterine breech position or abnormal neonatal hip exam). Participants may continue in the study provided that the nature, severity, and duration of the illness are recorded. Examples of minor illnesses for mothers that will be considered adverse events include mastitis, urinary tract infections, and surgical wound infections. Medications are allowed for treatment of these conditions in accordance with the judgment of the responsible study physician.

Documentation of an adverse event will be recorded on an Adverse Event Report Form and will include the following information:

1. Description of the illness
2. Dates of illness
3. Treatment of illness and dates (medications, doses, and dose frequency)
4. Whether emergency treatment or hospitalization was required
5. Treatment outcome

Though neonatal re-hospitalizations are an outcome measure for the study, they will be treated as serious adverse events (SAEs). Expected causes of re-hospitalizations are included in other portions of this protocol. The SAE rate for neonates is expected to be <5%.

C. CRITERIA FOR DISCONTINUING SUBJECTS FROM THE STUDY

Subjects who cannot be contacted after repeated attempts by phone will be sent a letter by mail asking them to contact the study staff. If this letter is not responded to within 2 weeks, the subject will be discontinued from the study.

D. DROPOUT STATUS

Any family who withdraws consent to participate will be assigned dropout status.

VI. DATA SAFETY AND MONITORING PLAN

A. PROTECTION OF HUMAN SUBJECTS

For this randomized trial examining the effect of different feeding strategies in infancy, we do not anticipate any medical risks for enrolled participants beyond the usual risks for mothers and infants in the immediate postpartum period. However, it is possible that early limited formula affects breastfeeding duration, so that either our intervention group or our control group might eventually have reduced breastfeeding duration, which could potentially affect their receipt of the health benefits associated with breastfeeding. We will therefore undertake a midcourse review halfway through enrollment to assess the data. We anticipate that recruitment and enrollment for this project will take 12 months, and we therefore anticipate reaching 50% enrollment at about 6 months. Since, after 6 months of enrollment, few of our enrolled participants will have reached our primary outcome of breastfeeding at 6 months, our midcourse review will assess rates of breastfeeding at 1 month. When 50% of our participants (82 participants) have completed 1-month follow-up, Drs. Flaherman, Paul, McCulloch and Cabana will examine the accrued data for data quality and completeness and will assess whether our intervention has had a significant effect on breastfeeding duration through 1 month. If our midcourse review shows that our intervention has had a significant effect on breastfeeding prevalence at 1 month, we will revise our consent form to include specific information about the potential for shorter breastfeeding duration at 1 month based on treatment assignment. Dr. Flaherman will take responsibility for all adverse events and serious adverse events and will report any of these within 24 hours to the UCSF Committee on Human Research, the Pennsylvania State Medical College Institutional Review Board and the Maternal Child Health Bureau.

In addition, because our study assesses maternal mental health outcomes, we will undertake a limited review of data completeness and quality once 10% of our participants have completed their final study mental health assessment at 1 month postpartum. This will enable any problems assessing maternal mental health to be identified in a timely fashion. If we identify systematic sources of incomplete data regarding mental health, we will repeat training of outcomes assessment for our research staff and reassess data completeness and quality in a similar fashion once the next 10% of participants have completed 1-month follow-up.

B. INCLUSION OF WOMEN AND MINORITIES

The ELF study will enroll breastfeeding women and their healthy term newborns. We will not be able to enroll fathers since males cannot breastfeed. We anticipate that about half of infants will be female. We will recruit ELF participants from the nurseries and postpartum wards at UCSF Medical Center and Penn State Hershey Medical Center. Based on our preliminary data, approximately half of our participants will be non-Hispanic white, and approximately half will be either Hispanic or non-white. Our two previous randomized trials of breastfeeding newborns at UCSF recruited participants with the following racial/ethnic distribution: 44% Asian, 23% white non-Hispanic, 20% white Hispanic, 10% African-American, 3% Pacific Islander, 0% American Indian/Alaskan Native. Our previous randomized trial of newborns at Penn State recruited participants with the following racial/ethnic distribution: 84% non-Hispanic white, 6% Black, 4% Hispanic, 4% Asian, 0% Pacific Islander and 0% American Indian/Alaskan Native.

C. INCLUSION OF CHILDREN

Improving outcomes for newborns is the main objective of this trial and therefore this population will be primarily studied.

VII. COST, LIABILITY, AND PAYMENT

There is no cost to the participating subjects. UCSF will mail each family a $20 gift card upon completion of each follow-up call at 1 week and at 1, 3, 6 and 12 months, for a total of $100 and a $5 gift card upon receipt of each stool collected at 1 week and 1 month (UCSF only).

VIII. STATISTICAL DESIGN AND ANALYSIS

A. DATA RECORDING AND DATA MANAGEMENT

Research staff will record participant data on the data collection forms, review the forms for completeness and legibility and will use password-encrypted Research Electronic Data Capture to allow entry on site at enrollment and immediately after each follow-up. This will further allow transfer of data between Penn State and UCSF. We will de-identify the data and transfer into Stata SE 11.2 (Stata Inc., College Station, TX) for analysis.

B. RANDOMIZATION AND STRATIFICATION

Michele Marini, MS, an independent biostatistician not otherwise affiliated with the study, will develop the randomization scheme using permuted blocks. The allocation sequence for randomization will be generated by an independent statistician through a secure computerized allocation system using a block randomization technique with randomly permuted blocks of 2 and 4 participants stratified on site, income (<200% Federal Poverty Level (FPL) or ≥200% FPL) and parity (primiparous or multiparous). As a result, the nurse will not have any foreknowledge of group assignment.

After entering the secure Microsoft Excel application and entering the delivery type, a randomization assignment (either ELF or safety education) will be returned for the mother-infant dyad. *Thus, randomization will occur after consent has been obtained and after lactation education has been completed.* Of note, though the stratifying variable will yield 3 strata with unequal numbers between strata, within each individual stratum there will be approximately equal numbers and balance between the treatment groups.

C. SAMPLE SIZE, POWER CALCULATIONS, AND STATISTICAL ANALYSIS

Based on the data from PI Flaherman's pilot study where breastfeeding rates were 40% higher for mothers and infants who received ELF than for those who were assigned to control, 74 mother-infant dyads are required in each arm of the randomization (148 in both arms) to prospectively demonstrate 40% increase in breastfeeding rates at 6 months with 90% statistical power and α=0.05. These calculations are based on the chi-square test. We will also attempt to analyze the data using a Cox proportional hazards model, which may have slightly greater power to detect a difference. Included in the calculation of these figures is the assumption that currently, many mother-infant pairs are advised to breastfeed exclusively but instead use some formula, usually in an unstructured manner. This crossover of assignment has been considered, and the sample size calculation reflects the fact that similar crossover occurred in our pilot study. A low dropout rate is anticipated given the low rate in previous similar studies, and the fact that patients will be knowingly enrolling in a research study involving the assessment of breastfeeding. In order to account for the possibility of 10% dropout, we will recruit 164 infants to have final follow-up on at least 148.

For the chief secondary outcome, maternal anxiety, the required sample size is 155 per cohort to have 90% statistical power and α=0.05 to test a 5-point difference in maternal state anxiety as measured by the STAI. Since anxiety outcomes will only be assessed in the first month of the study, we anticipate that enrolling 164 mothers will allow us to assess outcomes on anxiety for at least 155 mothers.

This study also seeks to examine the effect of ELF on health care utilization. Assessment of these will also occur in the first month only, when we estimate 95% follow-up, giving 155 outcomes. In site PI Paul's NITTANY study, 42% of newborns had additional health care utilization beyond an assigned study visit in the first 14 days.[98] Our sample size will therefore have adequate power to detect a 25% reduction in health care utilization. In NITTANY, mean scores for the Satisfaction with Maternal and Newborn Health Care Measure were 47.9 ± 7.1. Therefore, the ELF study will have adequate power to detect a 4-point difference (out of 55 possible) in satisfaction with quality of care.

D. ANALYTIC PLAN FOR MAJOR OUTCOMES

All primary statistical analyses will invoke the intent-to-treat paradigm; i.e., based on the randomized assignment to ELF or continued exclusive breastfeeding and regardless of actual treatment received, protocol violations, etc. A major study consideration is that many infants who are randomly assigned to exclusive breastfeeding at 18-72 hours will, in fact, actually receive formula at some point during the first week. In our pilot, about 50% of those who were initially randomly assigned to exclusive breastfeeding did receive formula

in the first week. This is consistent with national statistics, which show that about half of breastfed infants receive formula in the first week.[15] Our study hypothesizes that such unstructured formula use, which is common in the population as a whole and more common in babies with rapid early weight loss, may cause significantly worse breastfeeding outcomes than the carefully managed formula in the ELF intervention. The purpose of this trial is to compare the use of ELF with the current standard of care of recommending exclusive breastfeeding, with the recommendation followed by some and not by others. Therefore, analysis for most of our outcomes, including our primary outcome of breastfeeding duration at 6 months, will be intention-to-treat, which will inform the primary public health policy question of whether recommending against formula during the birth hospitalization improves breastfeeding duration.

We will use chi-square analysis to report the effect of ELF on our outcomes of breastfeeding at 6 and 12 months and breastfeeding without formula at 3 months. For each of the outcomes that assess the effect of ELF on breastfeeding duration, we will also attempt a Cox proportional hazards model. Using a Cox model adjusting for parity, race, ethnicity, income and delivery method, we will check for a lack of proportional hazards by including a time-varying interaction term in our predictor variables to identify any potential interaction between time and our primary predictor, use of ELF. We will then test the time-varying interaction terms and include them in the analysis to accommodate non-proportional hazards. We will use Student's t-test to assess the effect of ELF on the total volume of formula used in the first week and on maternal anxiety in the first week and the first month. We will also use multivariate linear regression to examine the effect of ELF on maternal anxiety after adjusting for parity, race, ethnicity, prior breastfeeding experience, income and method of delivery and to examine the effect of maternal anxiety on breastfeeding rates at 6 and 12 months adjusting for the same covariates.

Although most of our analyses will be conducted using an intention to treat approach, we will also conduct a limited as-treated cohort analysis to examine the effect of any type of formula use on health care utilization, because health care utilization may be more affected by whether or not any formula was used than by whether it was used on-protocol or off-protocol. Newborns should have at least one outpatient health care visit in the first month.[111] Therefore, for the outcome of health care utilization, we will use chi-square testing to examine the effect of ELF on whether or not ≥2 utilizations occurred. We will use Student's t-test to examine the effect of ELF on maternal satisfaction with quality of care.

Missing data: Loss to follow-up is an important concern for our study since mothers will be at a time of life with much change. We have learned how to maintain follow-up from our previous studies by using the following techniques: obtaining multiple phone numbers, obtaining the phone number of a contact who does not live with the participant, using a dedicated call-back number and multiple reminder calls. We have also found that our detailed assessment of breastfeeding information offers an opportunity to develop an emotional bond with participants that improves retention. To protect further against loss to follow-up for breastfeeding duration, we will obtain permission at enrollment to request medical records for babies with missing data to gain information on breastfeeding duration and formula use.

If there are participants for whom the primary outcome of breastfeeding duration remains unknown, we will compare rates of drop-out between the study arms and use a chi-square test to report whether follow-up is differential. We will also compare mothers with complete follow-up with mothers with incomplete follow-up using the validated Breastfeeding Attrition Prediction Tool to generate a likelihood of breastfeeding discontinuation,[112] and will use ANOVA to report whether mothers with missing follow-up had a higher *a priori* likelihood of breastfeeding discontinuation. For additional missing data not related to breastfeeding duration, we will use multiple imputation techniques to complete our analysis.

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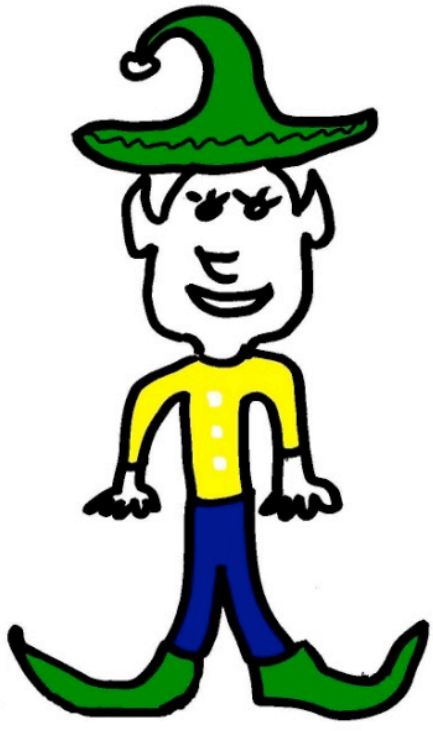
Appendix I

Breastfeeding Education for Mothers Enrolled in the Early Limited Formula (ELF) Study

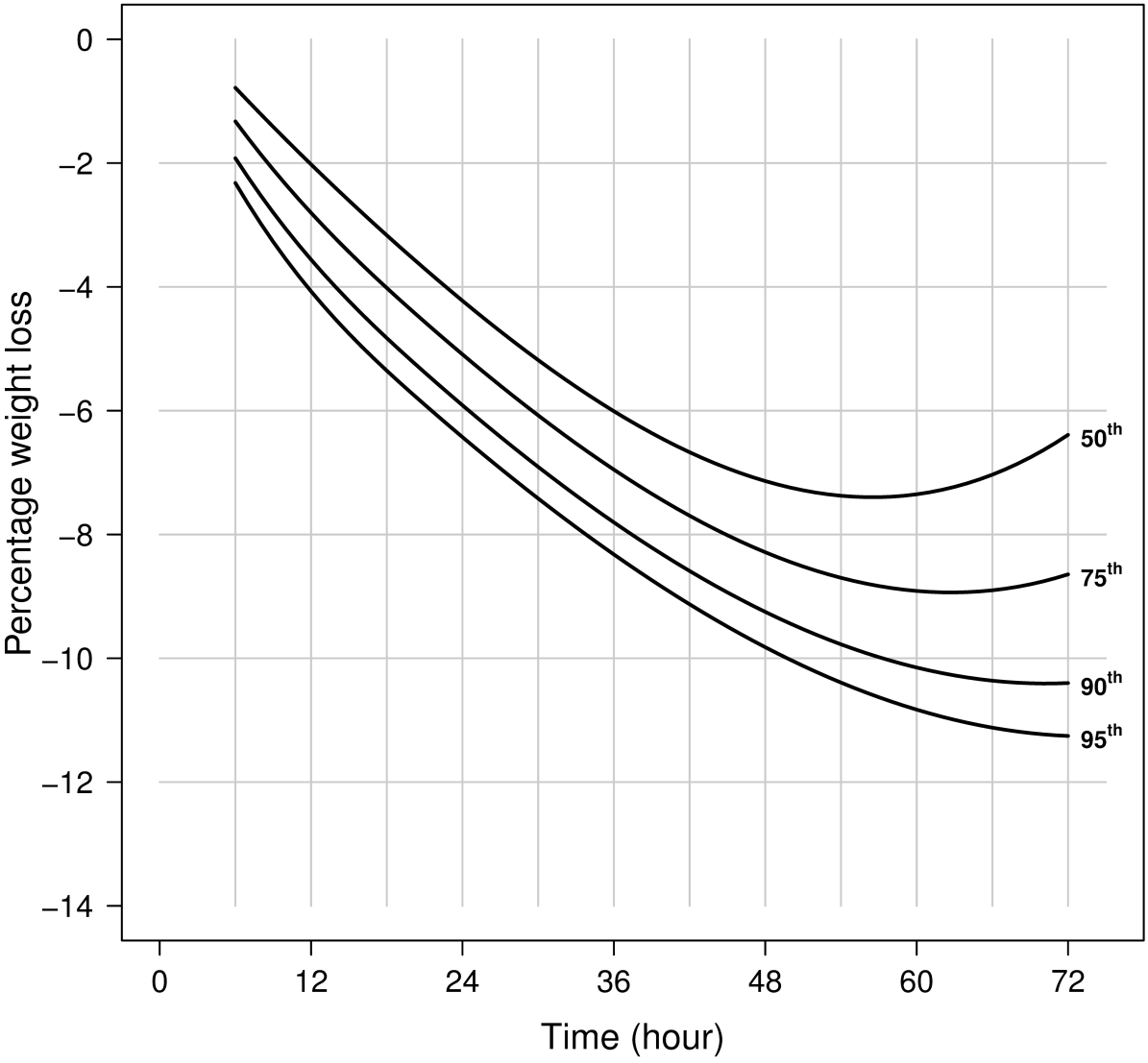
Thank you for enrolling in the Early Limited Formula (ELF) Study. Your participation will help us learn more about how to give each baby the best possible start with breastfeeding.

- Breastfeeding is a natural process, but getting started is not always easy. Here are some suggestions to help you on your way!
- For the first few weeks after birth, breastfeed 8-12 times in each 24 hours. This averages out to about one feeding every 2-3 hours, but sometimes newborns feed several times in a brief period and then sleep for a bit longer.
- Newborns will generally breastfeed for about 10-20 minutes per breast.
- Your newborn has important hunger signs. These include: opening his or her eyes, crying, sticking out his or her tongue and turning his or her head towards one side or from side to side. If it's been more than an hour since you fed your baby and you see these signs, consider feeding your baby.
- Make sure you are comfortable before you start to breastfeed. If you are sitting down, make sure you have support for your back and arms.
- Your baby should latch with a wide-open mouth, taking as much of your areola (deeply colored circle around your nipple) into his or her mouth as possible.
- If your baby is not interested in latching, try expressing a little bit of colostrum by hand and see if that helps with the latch
- In the beginning of breastfeeding, your breasts will make colostrum, a yellowish/orange liquid that has very important vitamins for your baby. When your baby is 2-5 days old, you will begin production of large volumes of mature breast milk.
- Before mature milk production begins, babies lose some weight each day.
- Before you make mature milk, your baby will urinate and stool only a few times per day. Once your mature milk comes, your baby should urinate and stool about 8 times per day.



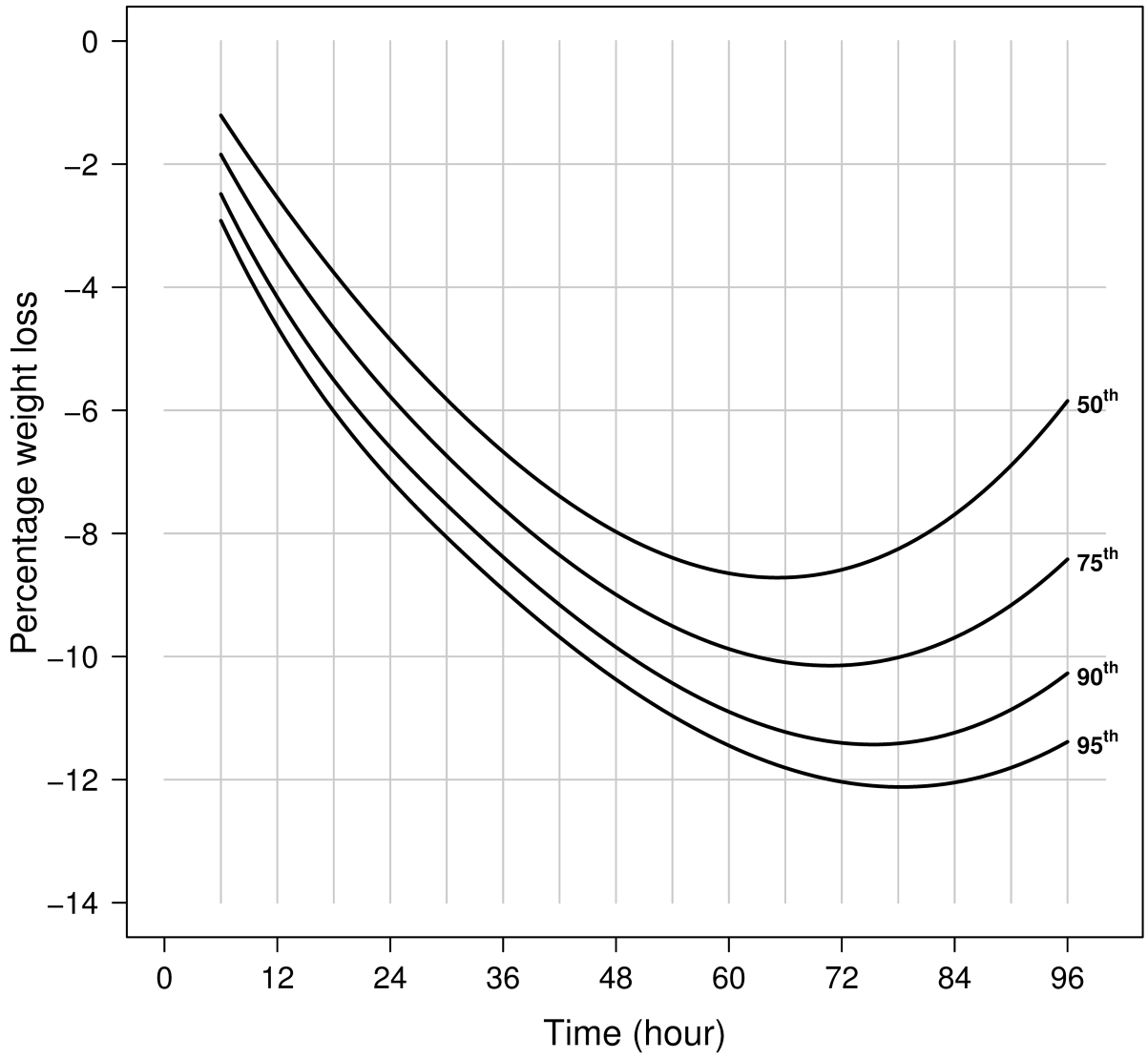
Appendix IIa

Estimated percentile curves of percent weight loss by time after birth for vaginal deliveries



Appendix IIb.

Estimated percentile curves of percent weight loss by time after birth for Cesarean deliveries



University of California
San Francisco

Human Research Protection Program
Committee on Human Research

Notification of Expedited Review Approval

Principal Investigator
Valerie J Flaherman, MD

Co-Principal Investigator

Type of Submission: Submission Response for Modification Form
Study Title: The Early Limited Formula (ELF) Study

IRB #: 14-13484
Reference #: 152897

Committee of Record: Laurel Heights Panel

Study Risk Assignment: Minimal

Approval Date: 12/15/2015 **Expiration Date:** 06/13/2016

All changes to a study must receive CHR approval before they are implemented. Follow the modification request instructions. The only exception to the requirement for prior CHR review and approval is when the changes are necessary to eliminate apparent immediate hazards to the subject (45 CFR 46.103.b.4, 21 CFR 56.108.a). In such cases, report the actions taken by following these instructions.

Expiration Notice: The iRIS system will generate an email notification eight weeks prior to the expiration of this study's approval. However, it is your responsibility to ensure that an application for continuing review approval has been submitted by the required time. In addition, you are required to submit a study closeout report at the completion of the project.

Approved Documents: To obtain a list of documents that were approved with this submission, follow these steps: Go to My Studies and open the study – Click on Submissions History – Go to Completed Submissions – Locate this submission and click on the Details button to view a list of submitted documents and their outcomes.

For a list of all currently approved documents, follow these steps: Go to My Studies and open the study – Click on Informed Consent to obtain a list of approved consent documents and Other Study Documents for a list of other approved documents.

San Francisco Veterans Affairs Medical Center (SFVAMC): If the SFVAMC is engaged in this research, you must secure approval of the VA Research & Development Committee in addition to CHR approval and follow all applicable VA and other federal requirements. The CHR website has more information.

1) Cover Page

Grant #R40MC26820
PI: Valerie Flaherman, MD, MPH, University of California, San Francisco
Project Title: The Early Limited Formula Study
Project start and end dates: 4/08/14-3/31/18
Yes, embargo needed

2) Introduction

Breastfeeding provides many important health benefits to mothers and babies, and longer duration of breastfeeding is associated with greater benefit. However, most mothers and babies who initiate breastfeeding stop well before the recommended duration of 12 months. Early breastfeeding problems occurring in the first few days after birth can have a major impact on overall breastfeeding duration. One challenge for mothers who initiate breastfeeding is that immediately after birth, mothers produce only about 1-5 mL of milk per feeding, and thus exclusively breastfed newborns typically lose weight until copious mature milk production begins at about 2-5 days of age. When such weight loss is pronounced, it can lead to increased healthcare utilization, maternal anxiety and breastfeeding cessation. Using formula along with breastfeeding can decrease healthcare utilization and may ameliorate anxiety, but has been strongly associated with reduced breastfeeding duration in multiple observational studies. For this reason, current public health efforts have focused on discharging newborns with no formula use, whatsoever. Previous work by our research group had shown that the brief, temporary use of small amounts of formula helped infants with rapid early weight loss overcome early breastfeeding problems. The Early, Limited Formula (ELF) Study was conducted to confirm or refute these results in a randomized controlled trial enrolling 164 exclusively breastfeeding dyads. Infants enrolled in the ELF study were randomly assigned either to receive ELF (10 mL formula after each breastfeeding, discontinued at the onset of copious maternal milk production) or to continue exclusive breastfeeding. The ELF study followed the enrolled population for 12 months to determine the effect of ELF on breastfeeding duration, maternal experience and healthcare utilization.

3) Study Design and Methods

The ELF Study was a randomized controlled trial that enrolled 164 mother-newborn dyads at the University of California San Francisco (UCSF) Medical Center and at Penn State Hershey Medical Center (HMC). Infants were eligible if they were 24-72 hours old, exclusively breastfed, born healthy at term and had lost ≥75th percentile of birth weight for hour of age. Mothers were eligible if they were ≥18 years old and English-speaking. During the maternity and newborn hospital stay at UCSF and HMC, study personnel identified eligible mothers and babies through a review of the electronic medical record. Once dyads were identified as meeting the inclusion criteria, informed consent was obtained from the mother for both herself and her infant.
To assess outcomes, the ELF Study used the following instruments: 1) breastfeeding prevalence at 1 week and 1, 3, 6 and 12 months of age was assessed using items modified from the CDC's Infant Feeding Practices Study; 2) breastfeeding self-efficacy at baseline and at 1 week was assessed using a modified version of the Breastfeeding Self-Efficacy Scale—Short Form; 3) maternal anxiety at baseline, 1 week and 1 month was assessed by the State Trait Anxiety Inventory; and 4) maternal depression at baseline, 1 week and 1 month was assessed using the Edinburg Postnatal Depression Scale.

All analyses were conducted in an intent-to-treat manner. We analyzed the effect of ELF on our primary outcome, breastfeeding through 6 months, using chi-square testing. We analyzed the effect of ELF on duration of breastfeeding using Cox proportional hazards analysis. We analyzed the effect of ELF on maternal anxiety as a continuous measure using Student's t-test and as a dichotomized measure using chi-square testing. We analyzed the effect of ELF on neonatal readmission using Fisher's exact test.

At 1 week of age, 96% of ELF infants and 94% of control infants were still breastfeeding ($p>0.5$); readmission occurred for 4 (5%) control infants and 0 (0%) ELF infants ($p=0.06$). At 1

month of age, 87% of ELF infants and 90% of control infants were still breastfeeding (p>0.5); 55% of ELF infants and 66% of controls were breastfeeding without formula (p=0.18). Readmission through 1 month of age occurred for 5 (6%) of control infants and 1 (1%) of ELF infants.

The primary outcome of this study was breastfeeding prevalence at 6 months, which did not differ between ELF (63%) and control newborns (76%) (p>0.05). However, breastfeeding prevalence at 12 months was lower among ELF (28%) newborns compared to controls (46%) (p=0.03), and overall duration of breastfeeding through 12 months was reduced for ELF newborns compared to controls (hazard ratio (HR) 0.65 (0.43, 0.97)). In multivariate proportional hazards analysis, married status, intended months breastfeeding duration, enrollment in San Francisco and formula use at 1 week of age were highly associated with breastfeeding duration with HRs of 0.36 (0.21, 0.62), HR 0.91 (0.85, 0.96), HR 0.41 (0.25, 0.70) and 4.42 (2.55, 7.64), respectively; treatment assignment was not correlated with breastfeeding duration in this model.

Our study showed that using ELF did not impact maternal anxiety, depression, breastfeeding self-efficacy or breastfeeding rates in the first 6 months after birth, and might potentially have had a beneficial impact on neonatal readmission. However, in this study, ELF reduced breastfeeding rates at 12 months of age. These results are challenging to interpret, because since median duration of use of ELF was 2 days, it is unclear how ELF could have had a deleterious impact on breastfeeding prevalence at 12 months without impacting maternal experience or breastfeeding prevalence at earlier time points. Our analysis of the data is ongoing to understand these findings.

Because infants who had been randomly assigned to ELF as newborns were less likely to breastfeed at 12 months of age than those randomly assigned to controls, any beneficial effect of ELF on neonatal healthcare utilization should be balanced against a potentially deleterious effect on breastfeeding through 12 months. Because formula use at 1 week of age had a strong negative correlation with breastfeeding outcomes at 6 and at 12 months in our study, we strongly recommend that if formula is used in the first few days of birth to ameliorate morbidity, it should be stopped by 1 week of age if possible to help support ongoing breastfeeding.

Our study had several important limitations. First, newborns enrolled in our study had weight loss ≥75th population centile for hour of age, and our results therefore do not necessarily apply to newborns with less pronounced weight loss. Second, mothers enrolled in our study were open to either supplementation with formula or to continued exclusive breastfeeding. Thus, our results do not necessarily apply to mothers who prefer to use formula or prefer to breastfeed exclusively. Third, mothers randomly assigned to ELF were at baseline less likely to be married and had shorter intended duration of breastfeeding than control mothers. Since being married and having longer intended duration of breastfeeding were both strongly associated with breastfeeding duration at 12 months, it is possible that our study results are partially influenced by confounding from the uneven baseline distribution of these variables.

In comparison with previous findings suggesting ELF might improve breastfeeding rates for newborns with pronounced weight loss, these new study results suggest that ELF should not be used for the purpose of improving breastfeeding duration through 12 months. Consistent with previous literature in this area, the new findings support the possibility that approaches such as ELF may ameliorate neonatal morbidity and resultant healthcare utilization. ELF may be helpful to reduce the risk of neonatal readmission for newborns with pronounced weight loss. Any potential use of ELF to reduce the risk of neonatal readmission should therefore be balanced against a potential detrimental effect of ELF on breastfeeding rates through 12 months.

4) List of Products (peer-reviewed articles, books, chapters in books, conference presentations, etc.).

Published manuscript:
Flaherman VJ, Narayan N, Hartigan-O'Connor D, Cabana MD, Paul IM. The Effect of Early Limited Formula on Breastfeeding, Readmission and Intestinal Microbiota: A Randomized Clinical Trial. J Pediatrics. 2018 May;196:84-90

Manuscripts in preparation:
Flaherman VJ, Cabana MD, McCulloch CE, Paul IM. The Effect of Early Limited Formula on Breastfeeding Through 12 Months: A Randomized Clinical Trial.

Flaherman VJ, Cabana MD, Paul IM. Psychometric Characteristics of the Infant Satisfaction and Satiety Subscale.

Flaherman VJ, Luna R. Maternal Recall of Breastfeeding and Formula Supplementation in the First Year

Flaherman VJ. Reasons for Breastfeeding Cessation among Infants with Pronounced Weight Loss

Research conference presentations:

- Newborn Weight Loss: Towards a Stronger Evidence-Base for Evaluation and Management, Newborn Nursery Special Interest Group, Pediatric Academic Societies 2015 Annual Meeting

- Early Weight Loss Nomograms for Exclusively Breastfed Newborns Delivered Vaginally and By Cesarean, Academy of Breastfeeding Medicine 2016 Annual Meeting

- Randomized, Controlled Trial of Early Limited Formula (ELF) on Breastfeeding Duration, Pediatric Academic Societies 2018 Annual Meeting Platform Presentation

- The Effect of Brief Postnatal Formula Use on Intestinal Microbiota During the First Month After Birth, Pediatric Academic Societies 2018 Annual Meeting Platform Presentation

- Randomized, Controlled Trial of Early Limited Formula (ELF) on Breastfeeding Through 1 Month, Pediatric Academic Societies 2017 Annual Meeting Platform Presentation

5) Dissemination activities and plans beyond peer-reviewed publications

Dissemination activities beyond the above publications have included research conference presentations, clinical presentations, public health presentations, webinars and media coverage listed below:

Clinical presentations:

- *Breastfeeding and Formula: Towards an Evidence-Based Nursery, San Francisco General Hospital Grand Rounds*
- *Breastfeeding and Formula: Towards an Evidence-Based Nursery, Washington Hospital Grand Rounds, Fremont, CA*
- *Early Newborn Weight Loss and Its Relationship to Short- and Long-Term Breastfeeding Outcomes," Pediatric Grand Rounds, Kaiser Permanente San Francisco*
- *Breastfeeding and Formula: Towards an Evidence-Based Nursery, Children's Mercy Hospital, Kansas City, Missouri*
- *The Early Limited Formula Study: Improving the Transition from Hospital to Home for Newborns with Pronounced Weight Loss, Perspectives on Feeding and Sleep: From Pregnancy to Playgrounds, Amsterdam, NE*
- *Early Weight Loss Nomograms for Newborns Delivered Vaginally and By Cesarean, Konika Pediatrica, Yogykarta, Indonesia*

Public health presentations:

- *The Impact of Early Supplementation on Breastfeeding and Infant Health," San Francisco Breastfeeding Promotion Committee, Creating Healthy Families Conference*

Webinar:

- *Early Newborn Weight Loss and Its Relationship to Short- and Long-Term Breastfeeding Outcomes, New York City Department of Public Health*
- *The Early Limited Formula Study: Improving the Transition from Hospital to Home for Newborns with Pronounced Weight Loss, HRSA EnRich Webinar*

Media:

- *The Case for Rethinking Breastfeeding Goals, by Catherine Pearson, Huffington Post*
- *Adding Formula to Breast-Feeding May Help Some Newborns, by Nicholas Bakalar, New York Times, March 15, 2018*

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6) Describe plans to continue this line or program of research through additional external funding

We are currently conducting three funded studies continuing this line of research, and have applied for additional external funding to conduct others.

Funded studies:

Milk, Immune Function and Microbiota (MIMI)

The MIMI study has been funded by the UCSF Department of Pediatrics Clinical Translational Pilot Awards. MIMI is an observational study which enrolled 24 healthy breastfeeding term newborns during the birth hospitalization and followed them for 6 months collecting data on type of feeding, receipt of immunizations, immune function and intestinal microbiota at birth, 1 month, 3 months and 6 months of age. Additionally, at 1 week of age MIMI collected data on type of feeding and intestinal microbiota. MIMI follow up is now complete, with 23 out of 24 (95.8%) infants completing followup through 6 months. Specimens from MIMI are currently being analyzed in the laboratory of Dennis Hartigan-O'Connor, PhD, at UC Davis. The aims of MIMI are:

1: To examine the effect of combining formula feeding with breastfeeding on immune function. Using a panel-of-panels approach for simultaneous measurement of hundreds of immune cell phenotypes in a small sample volume, we are assessing the overall profile of immunologic development in study infants. We hypothesize that participants who receive formula in addition to breastfeeding will demonstrate delayed immunologic development and reduced vaccine responses compared to infants who breastfeed exclusively without formula.

2: To examine the association between intestinal microbiota and immune function. In this aim, we will assess the relationship between abundance of bacterial taxa, measured by 16S rRNA gene sequencing, and the immunologic profiles developed in Aim 1. In particular, we are interested in the possible relationship between abundance of Lactobacillus, Bacteriodes and Clostridia and the development of immune activation states and CD4+ T helper cell skewing. We will also use exploratory clustering approaches to test for broader relationships between intestinal microbial communities and phenotypic changes in immune cell subsets.

By analyzing the relationship between type of feeding, intestinal microbiota and immune development in the context of receipt of immunization, we hope to identify potential strategies for bolstering infant immune response to pathogens while modulating any response to potential allergens. Better understanding of the relationship between intestinal microbiota and infant immune development might lead to the development of interventions to foster beneficial intestinal microbiota that might bolster the beneficial effects of breastfeeding for breastfed infants or might attain some of the beneficial effects of breastfeeding for those who are unable to breastfeed.

Milk, Growth and Microbiota (MGM)

The MGM study is a randomized controlled trial funded by the Preterm Birth Initiative. MGM is currently enrolling 48 late preterm newborns between 34 0/7 weeks and 36 6/7 weeks gestation. Newborns are eligible for enrollment in the MGM study if their birth weight is ≥2100 gm, their mothers are not yet producing copious breast milk and they are currently breastfeeding but require supplementation. Enrolled newborns are randomly assigned to receive their supplementation either as standard infant formula or as donor breast milk from a certified milk bank. The randomly assigned supplement is provided by the study until the onset of copious maternal milk production or until 7 days of age. In outcome assessment, MGM collects data on type of feeding, infant weight at 24 and 48 hours after enrollment and at 1 week of age and intestinal microbiota at enrollment and at 1 week and 1 month of age. MGM has enrolled 17 of our target of 48 infants. Follow-up has been completed on 12 of these enrolled infants, with an

additional 5 infants completing followup within the next month. Specimens from MGM are currently being stored for batched analysis once specimen collection is complete. The aims of MGM are:

1: To compare the effect of donor milk vs. formula on growth for late preterm breastfeeding newborns through 1 week of age.

2: To compare the effect of donor milk vs. formula on intestinal microbiota for late preterm breastfeeding newborns through 1 month of age.

MGM will be the first study to report the effect of donor breast milk on outcomes for late preterm infants. Studies of donor milk for extremely preterm and very preterm infants have shown that donor milk can prevent necrotizing enterocolitis for these populations but may be associated with slower weight gain. Before donor breast milk can be recommended for use in late preterm infants, it will be important to show that it does not negatively impact weight gain for the late preterm population. Data from MGM will provide valuable evidence to guide supplementation decisions for these babies.

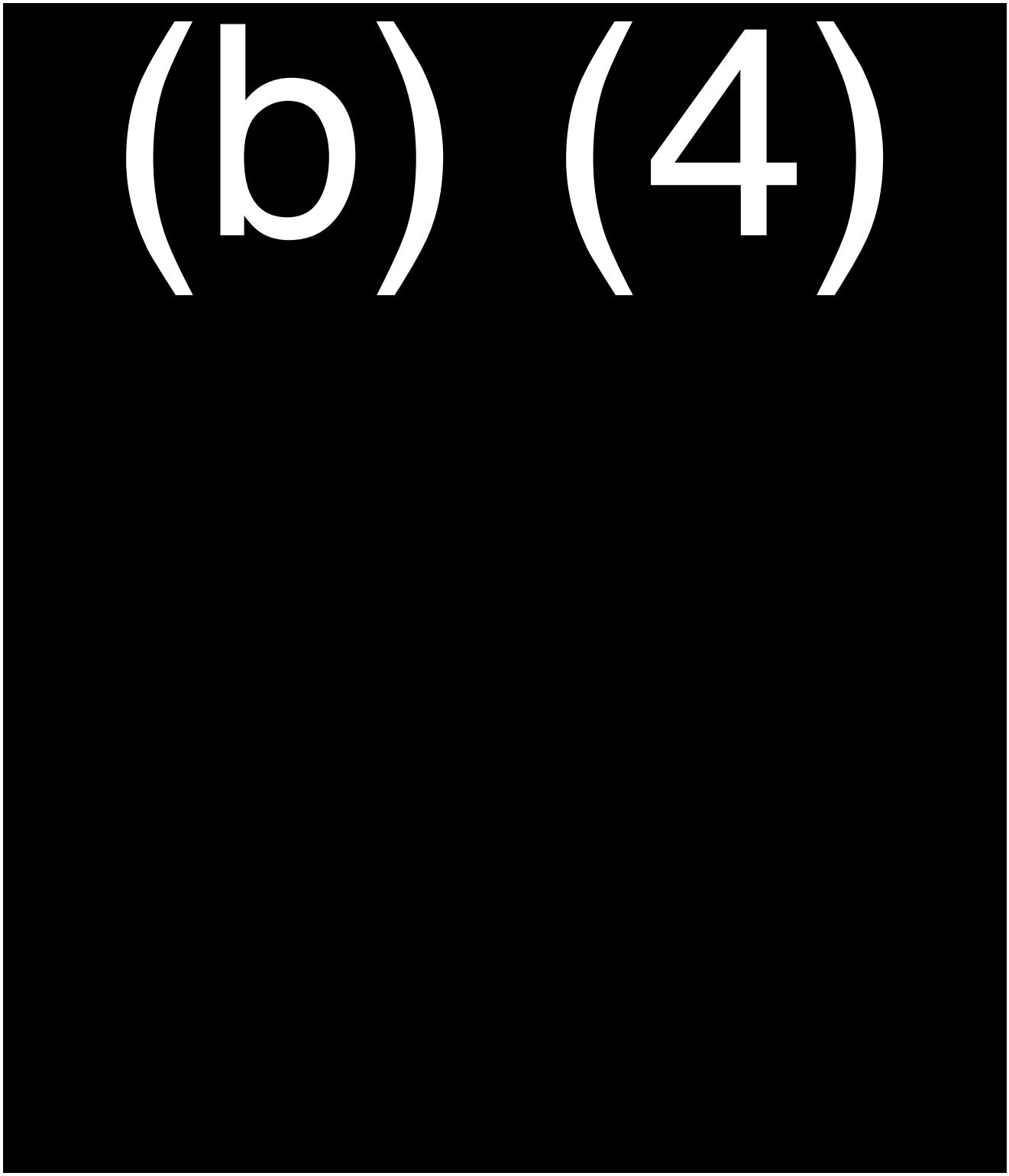
<u>Beginning with a Healthy Start: Reducing Non-Preventive Healthcare Utilization in the First Month</u>

Healthy Start is a randomized controlled trial funded by the UCSF Learning Healthcare System Demonstration Project initiative. The Healthy Start study will enroll all healthy in-born newborns at UCSF Benioff Children's Hospital who are admitted to the well newborn service. Newborns enrolled in Healthy Start will have electronic medical records randomly assigned either to depict daily weight change in the context of hour of age using the Newborn Weight Tool (Figure), or to usual care, displaying weight in grams and as a percent weight lost from birth weight. Those infants randomly assigned to display the Newborn Weight Tool will also have a banner displayed above their summary page that will guide users towards considering the risks and benefits of formula supplementation for newborns with weight loss ≥75th centile for hour of age (below the yellow line on NEWT). We anticipate enrolling approximately 2,400 newborns over the 11 months of this randomized trial. Outcomes to be assessed include length of stay during the birth hospitalization, neonatal readmission and any non-preventive healthcare utilization in the first month of life. We hope that the Healthy Start study will inform future efforts to integrate information on targeted formula use into the electronic medical record to allow for dissemination of evidence-based practices for infant feeding.

Figure: The Newborn Weight Tool

<u>Future studies:</u>

(b) (4)



7) Research Grants Impact Analysis

MCHB is working to demonstrate the impact of funded research grants to a variety of stakeholders. Using the table below, provide some information on the impact of your research grant:

No. of Research Sites[1]	Total No. of Studies[1]	Total No. of Participants ever Enrolled	No. of Peer-Reviewed Publications[2]	No. of Non-Peer Reviewed Publications[3]	Total No. of Researchers Involved in Research[4]	Total No. of Trainees Mentored[5]	No. of External Funding Apps Submitted	No. of External Funding Apps Received
2	1	328	1	0	5	6	6	2

Footnotes: [1]Limit data report from study inception to date; [2]Includes only published papers; [3]Includes conferences workshops, webinars, community dissemination products; [4]Includes all Investigators, Co-Investigators, Affiliates, and Researchers; [5]includes pre and postdoctoral mentees, if available, include demographic information.

September 24, 2021

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Re: Redactions appeal, FOIA Request - Early Limited Formula for Treating Lactation Concerns (ELF-TLC) clinical trial documents and data, Request Case Number 21F164

Dear Ms. Maloney:

This letter responds to your agency's September 8, 2021 response to my FOIA request dated April 30, 2021, requesting documents and data relating to the Early Limited Formula for Treating Lactation Concerns (ELF-TLC) clinical trial. Thank you for releasing responsive records, and for addressing the FOIA's questions, including providing the additional background information that HRSA's Maternal and Child Health Bureau provided. I sincerely appreciate your time and assistance.

In addition, I would like to appeal the redaction component of the agency's response. This appeal makes three claims that should be considered separately. First, the FOIA exemption 4 trade secret decision has been overly broadly applied. Second, even if it had been correctly applied, exemption 4 would need to be balanced against the public interest. Third, the agency should consider whether it is the proper role of the agency or of the public to weigh these interests in this case.

Justifying redaction, the agency stated: "Exemption 4 protects "trade secrets and commercial or financial information obtained from a person [that is] privileged or confidential." The withheld information is "commercial or financial information". The entity that supplied this information (the submitter) is considered a person, because the term "person," under the FOIA, includes a wide range of entities including "universities"."

Keeping a researcher's study designs private does not comport with a typical understanding of commercial interest. The researcher did not disclose any commercial interest in her relevant publications on the study at issue. That would have been considered a conflict of interest requiring disclosure.

Two of her co-authors did disclose such interests. One reported consultancy for Nestle and another for Johnson & Johnson. However, their commercial interests are not protected here, since they did not receive the HRSA grant that made the IRB protocol accessible under FOIA. It is also unclear what their relevant commercial interests would be, since the research does not compare formula brands or otherwise promote the benefit of one product over another. Comparative or competitive commercial advantage in that sense is irrelevant to this research.

The agency's response also specifically mentions universities. But a university cannot be said to have a commercial interest in protecting its researchers' future research designs, because academics routinely circulate their designs in advance of running studies. Indeed, such designs are often a recommended, standard part of publications such as meta-analyses, or specified in the discussion or

conclusion sections of articles that report original results as possible future research. This type of public disclosure is an integral part of routine academic work. Thus, there is no protected commercial interest on the part of the university that disclosure would harm. To the contrary, this type of routine academic work is a key part of how researchers usually obtain the publications and grants from which they and their universities benefit.

In favor of redaction, HRSA also argues "the submitter does not customarily release this information to the public and HRSA provided the submitter an assurance of confidentiality; therefore, the information is confidential for the purposes of Exemption 4." But again, researchers circulate their designs all the time in advance of running studies. That circulation may take the form of publications, seminar papers, and grant proposals, all of which may be public. There is no protected norm or expectation of confidentiality in the process of designing studies — particularly publicly funded studies. Rather, there are strong norms encouraging critical discussion to improve science, particularly when it involves human subjects, and particularly when those subjects are especially vulnerable, as in the case of exclusively breastfed newborns who have already lost substantial weight due to insufficient milk intake. Indeed, it is difficult to imagine a more helpless group of individuals than starving newborns. Furthermore, Exemption 4 is not about expectations of confidentiality; it is about commercially sensitive information, a category that is not applicable in this context.

Overall, the agency's application of FOIA Exemption 4 to protect commercially sensitive information in this case was incorrect. This decision misapplied an overly broad interpretation of the exemption that is not in general use as it concerns research, universities, or academic work, and conflated the distinct concepts of competitive advantage and confidentiality. Both concepts are irrelevant: Competitive advantage is irrelevant in the case of future research designs and confidentiality is not at issue in Exemption 4. This appeal asks the agency to rectify this mistake.

If instead the agency rules that the applied definition of commercially sensitive information was indeed correct, it must still consider whether disclosure is required nonetheless. Disclosure may still be required to serve a greater public interest. This interest should be weighed against the alleged potential competitive harm of disclosure in an independent evaluation performed by the agency and not the investigator/institution that requested the redactions. The agency should also consider whether the central balancing question — on one hand, redaction to prevent alleged potential competitive harm to the commercial interests of a public university and/or associated researcher who received federal funds for relevant research, versus, on the other hand, public disclosure in the public interest to prevent harm to newborns from future research — is not a question for the democratic public rather than the agency itself to properly answer.

The remainder of this appeal letter explains why disclosure is required in this case to serve a greater public interest than the applied definition of protecting trade secrets. This explanation should be evaluated separately from this appeal's first claim, that the agency overly broadly applied Exemption 4, and its third claim, that it is the role of the public and not the agency to decide in this case whether an alleged potential competitive harm is more important than protecting newborns from preventable harm in the context of federally funded medical experiments.

The documents that HHS did release in response to this FOIA request show that the investigators in the Early Limited Formula trial failed to inform their IRB in the protocol of associated, preventable risks of serious harm to newborns. This suggests the IRB subsequently failed to consider or apply Section 46.406 Subpart D (Additional Protections for Children Involved as Subjects in Research) of the Federal Policy for the Protection of Human Subjects, since it would not have known that it was relevant (though it was). It also suggests investigators failed to inform parents of these risks, and thus failed to obtain valid informed consent as required by applicable laws and policies. The

agency's response to this FOIA also indicated investigators failed to report adverse events to the U.S. Department of Health & Human Services, which funded the study. The associated risks, as well as these investigators' apparent failures to communicate about them with their IRB, study participants, and HHS, are described with citation to the documentation that HHS disclosed in my recent peer-reviewed article, "Breastfeeding Insufficiencies: Common and Preventable Harm to Neonates," *Cureus,* **(insert complete citation and link).**

Specifically, the agency's response to this FOIA stated "In response to item 2, the trial did not report adverse events. In the protocol, the grantee did not expect any adverse events" (p. 2). However, records the agency disclosed shows the grantee knew hyperbilirubinemia was a risk, and numerous neonatal rehospitalizations for hyperbilirubinemia resulted; the grantee expected and observed adverse events. The researchers knew that exclusively breastfed newborns who had already lost substantial weight were in medical danger from insufficient nutrition and hydration, and repeatedly ran studies that insufficiently communicated about and failed to mitigate that danger. Their resultant publications show that preventable harm resulted.

Ironically, it is actually this very harm that this research purported to seek to minimize by creating an evidence base showing that early limited formula supplementation for exclusively breastfed newborns who have lost substantial weight does not hurt breastfeeding rates later — a hypothesis that this study unintentionally disconfirmed, although the investigators had expected to replicate their prior, smaller ELF study supporting it. The investigators cannot simultaneously argue that their research was important to change clinical practice that endangers newborns, and that their study designs did not endanger newborns. Yet that is what correspondence with their IRB Director (available on request) seems to imply may have occurred. In any event, the investigators are experts in the very preventable harm to newborns that their protocol conspicuously failed to describe under risks. This is concerning.

Hospital readmissions for hyperbilirubinemia are adverse events according to the grantee's IRB protocol's definition, as well as any generally accepted definition of adverse events. This is how the grantee, Dr. Valerie Flaherman, defined adverse events in her IRB protocol: "Adverse events that will be recorded include jaundice/hyperbilirubinemia requiring phototherapy, intravenous fluid administration, and laboratory evaluations of any kind not related to a prenatal diagnosis (e.g. renal ultrasound to follow up on antenatal hydronephrosis, hip ultrasound due to intrauterine breech position or abnormal neonatal hip exam)." Adverse events associated with the trial meet this definition.

Before this study was run, its design was known to be risky and contentious: Dr. Caroline Chantry, a past President of the Academy of Breastfeeding Medicine, criticized the appropriateness of this design in a 2014 publication. That public criticism by a leading expert in the relevant field predated the version of the ELF trial that HHS funded. It referred to an earlier, smaller version of this study. The fact that the researchers attempted to replicate the earlier study in spite of this criticism, without additional safeguards, without disclosing the relevant risks and related criticism to their IRB, probably also without disclosing the relevant risks to parents of newborns in the study (although without access to the informed consent form that HHS says it does not have, one cannot know for certain) — and without even reporting adverse events to HHS even though they are reported in the publication record, shows that these researchers are capable of again running future studies that risk preventable harm to newborns without appropriate human subjects protections and oversight from their institutions, study participants, grantors, and the public that funded this research.

I am concerned that, given these researchers' proven record of repeatedly endangering newborns in their research, HHS's withholding of related future study designs perpetuates the risk that the same researchers will endanger newborns in the same or a similar way in their research again. Whether

this is an acceptable risk in federally funded research is a question that should be subject to public discussion in a democracy. The purpose of FOIA is to enhance public understanding of government activities, including funding of research, in a way that serves the public interest, enables democratic oversight, and upholds the law to protect those who cannot protect themselves. Overly broad application of the FOIA exemption 4 in this case undermines that purpose, violating the first principles of upholding the law, protecting some of the most vulnerable people imaginable (newborn babies) from preventable harm, and enabling democratic oversight of government operations and activities. Please disclose the redacted future study designs.

Thank you for your time, consideration, and assistance.

Best regards,
Vera Wilde

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