

1 It is also important to consider
2 the potential for regret. One possibility for
3 minimizing this potential is to enroll
4 subjects who have already undergone a
5 sterilization procedure. However, this needs
6 to be balanced against the possible risk of
7 post ablation tubal sterilization syndrome.

8 Another possibility is to limit
9 enrollment to older women, but this may limit
10 the generalizability of the study information
11 to the broader population intended for use
12 leaving the question of how the product will
13 be labeled and whether additional studies will
14 be needed prior to marketing.

15 These risks that need to be
16 balanced against the benefit, which in this
17 elective use study, is for lifestyle
18 preferences. This may be likened to a
19 cosmetic procedure, such as breast
20 augmentation, in that the patient is electing
21 the surgical procedure to improve or enhance
22 her lifestyle. This makes for a different

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1 evaluation of the risk/benefit analysis that
2 is required for every new clinical
3 investigation. This is the subject of another
4 one of our discussion questions.

5 The fourth guiding principle is
6 justice. To this end, the development plan
7 for this indication, as reflected in the
8 protocol study population, should avoid
9 exploitation of subjects. The risk should not
10 be born disproportionately by women who would
11 not be part of the intended use population and
12 economically disadvantaged women who are
13 unlikely to receive this therapy after
14 commercialization should not be targeted for
15 the clinical study.

16 We think that the conduct of this
17 elective use study will require careful
18 consideration of international issues and the
19 applicability of outside the U.S. subjects to
20 the U.S. population. This is a complex
21 ethical issue and we will encourage sponsors
22 to confer with FDA first before embarking on

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1 an international study.

2 That concludes my formal
3 presentation and I look forward to the Panel's
4 input on the discussion questions. Thank you.

5 CHAIR CEDARS: Thank you. We will
6 now proceed with the Open Public Hearing
7 Portion of the meeting. Both the Food and
8 Drug Administration and the public believe in
9 a transparent process for information
10 gathering and decision making. To insure such
11 transparency at the open public hearing
12 session of the Advisory Committee meeting, the
13 FDA believes it is important to understand the
14 context of any individual's presentation.

15 For this reason, the FDA encourages
16 you, the open public hearing or industry
17 speaker at the beginning of your written or
18 oral statement, to advise the Committee of any
19 financial relationship that you may have to
20 the sponsor, its products and, if known, its
21 direct competitors.

22 For example, this financial

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1 information may include the sponsor's payment
2 of your travel, lodging or other expenses with
3 connection of your attendance at the meeting.

4 Likewise, the FDA encourages you at the
5 beginning of your statement to advise the
6 Committee if you do not have any financial
7 relationships.

8 If you choose not to address the
9 issue of financial relationships at the
10 beginning of your statement, it will not
11 preclude you from speaking. Prior to the
12 meeting, we received two formal requests to
13 speak during today's open public hearing
14 session.

15 The first speaker will be Dr.
16 Arthur McCausland. If you would, please, come
17 forward to the microphone, we ask that you
18 speak clearly into the microphone and allow
19 the transcriptionist to provide an accurate
20 record of the meeting.

21 DR. ARTHUR McCAUSLAND: Thank you
22 very much. My name is Dr. Arthur McCausland.

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1 I'm a clinical professor of OB GYN at the
2 University of California at Davis Medical
3 School. My goal is to inform the FDA of the
4 long-term complications of endometrial
5 ablations to assure that patients who are
6 considering a cosmetic ablation are obtaining
7 an appropriate and informed consent.

8 And I forgot to tell you, I do not
9 have any financial conflict of interest here.

10 My son and I recently reviewed the
11 world literature and wrote a comprehensive
12 review article entitled "A Long-Term
13 Complications of Total Global Endometrial
14 Ablation" that was published in the Journal of
15 Minimally Invasive Gynecology just a couple of
16 months ago.

17 The long-term complications of
18 total ablations include central hematometra,
19 cornual hematometra, post ablation tubal
20 sterilization syndrome, which we call PATSS,
21 retrograde bleeding and potential delay in the
22 diagnosis of endometrial cancer.

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1 The goal of all total or global
2 ablations is to destroy the entire
3 endometrium. And that's for any of these
4 techniques. I will be calling these first
5 generation ablations and I will be calling the
6 second generation -- some people call first
7 generation more resectoscopic and the more
8 global techniques non-resectoscopic.

9 When you remove the entire
10 endometrium, you are exposing myometrium and
11 when you let your distention media out or
12 remove your instrument, these myometrial walls
13 collapse upon each other and have a natural
14 tendency to grow together. They usually grow
15 together in the stippled area in the periphery
16 and this often obstructs the cornual areas.
17 This is called an intrauterine contracture.
18 Some people call it intrauterine scarring.

19 As far as the second generation
20 global endometrial ablation, Roy found that
21 all heat-based thermal devices whether it is
22 balloon, ThermaChoice, Mesh, NovaSure or HTA

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1 or Microwave ablation, any of these that
2 destroy the endometrial lining can cause
3 scarring of the cavity. Scarring alters the
4 architecture of the endometrial cavity when
5 raw myometrial surfaces oppose each other and
6 heal.

7 Looking at the Essure/ThermaChoice
8 HSG Study, 33 percent ended up having
9 intrauterine synechiae and this was three
10 months after the procedure. And 17 percent
11 had severe scarring which was so severe they
12 were unable to confirm tubal occlusion. So
13 this study was stopped.

14 And the NovaSure HSG Study, Hopkins
15 found that intrauterine scarring increased
16 with time after the ablation. At three months
17 24 percent had mild synechiae, 33 percent had
18 filling defects. At six months, all had
19 synechiae and filling defects and at nine
20 months, there was one case that had complete
21 obliteration of the cavity.

22 So we are finding out that both

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1 first generation and second generation
2 ablations are causing significant intrauterine
3 scarring. And I will be mentioning in a few
4 minutes about how this scarring can obstruct
5 blood. And as you can see, it takes time for
6 this scarring and contracture to develop.

7 So we are finding that for
8 symptomatic obstructive blood to occur, it
9 takes two to three years. So any kind of
10 study that you are setting up that's going to
11 be looking at this issue has to be at least
12 three years long. Some of them take out to
13 seven years to occur.

14 This is looking at the
15 post-NovaSure, Essure, HSG. The one on the
16 left is at three months and you can see the
17 cavity is fairly open; however the right tube
18 was patent, so they repeated this at six
19 months and if you look up in this cornual area
20 and intrauterine area compared to here, you
21 begin to see this intrauterine contracture up
22 in the cornual area and in the intrauterine

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1 cavity.

2 This contracture and scarring
3 really has no clinical significance, except if
4 blood is or endometrium is trapped up in the
5 upper fundal cornual areas or intramural
6 oviduct above the scar. Lisa serially
7 sectioned the intramural oviduct in 300 uteri.
8 25 percent had endometrium in the intramural
9 portion of the tube. And this is showing the
10 endometrium in the intramural oviduct and no
11 ablation techniques gets to this tissue.

12 Turnbull did MRI of the uterus now
13 for total endometrial resection ablation. He
14 found that there is endometrial tissue
15 detected in 95 percent and this usually was up
16 in the upper fundal and cornual regions. He
17 found cornual hematometra in 18 percent. Two
18 had PATSS and 54 percent demonstrated
19 retrograde bleeding. In an MRI, you can tell
20 if peritoneal fluid is just serous fluid or
21 blood and this was blood.

22 This is a cornual section MRI of

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1 Turnbull showing the endometrium that was
2 either regenerating or persisting up in the
3 cornual areas and he found this in 95 percent
4 of patients. This is a cornual hematometra
5 that he saw in this section of the MRI and he
6 found this in 18 percent.

7 And I looked at the frequency of
8 symptomatic cornual hematometra in PATSS after
9 total Rollerball endometrial ablation. I
10 followed 50 patients for 10 years. Two ended
11 up having cornual hematometra, three had
12 cornual hematometra and PATSS for a 10 percent
13 incidence of these painful conditions. Nine
14 of the 50 patients had had a history of a
15 tubal ligation and three ended up with PATSS.

16 So that's an incidence of 33
17 percent in patients who have had an ablation
18 and a tubal ligation if you follow them out 10
19 years.

20 What's the pathophysiology or
21 cornual hematometra in PATSS? If the
22 endometrium that is persisting in the cornual

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1 area begins bleeding and obstructed, and is
2 obstructed, you'll get a cornual hematometra
3 and this blood can retrograde bleed into the
4 proximal tubal segment in somebody who has had
5 a tubal ligation. It distends that segment
6 and becomes very painful. A patient in this
7 situation who has not had a tubal, she will
8 have retrograde bleeding.

9 This is a cornual hematometra where
10 there is obstruction on both sides. So the
11 incidents following first generation ablations
12 for central hematometra, these are the
13 published incidents, it's 1 to 2 percent,
14 cornual hematometra 10 to 18 percent, PATSS in
15 patients who had a tubal ligation range from 6
16 to 33 percent.

17 As far as cornual hematometra in
18 PATSS after the newer global endometrial
19 ablations, there are cases of cornual
20 hematometra in PATSS that are being
21 voluntarily reported after balloon, microwave
22 and mesh electrol ablations to the MAUDE

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1 Database.

2 The incidence is unknown; however,
3 the ACOG Practice Bulletin entitled
4 "Endometrial Ablation," which was published
5 just this past May, states that there is at
6 least a 24 percent hysterectomy rate within
7 four years after both resectoscopic and
8 non-resectoscopic total endometrial ablations.

9 And Vilos looked at the indications
10 for hysterectomy after total ablations and he
11 found that 12 percent were for bleeding, 64
12 percent were for pain and 24 percent were for
13 both, so there is an 88 percent chance that
14 this had to do with pain also.

15 The diagnosis -- I just want to let
16 you know that 53 percent of these patients had
17 adenomyosis, but 47 percent did not.

18 CHAIR CEDARS: If I could ask you
19 to, please, wrap up?

20 DR. ARTHUR McCAUSLAND: I think I
21 talked to Michael and he said I could have 10
22 minutes.

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1 CHAIR CEDARS: And the 10 minute
2 are up, so I would like you to summarize,
3 please.

4 DR. ARTHUR McCAUSLAND: Oh, they
5 are? Well, let me get down to the bottom
6 here. I'm just saying it's harder to treat
7 PATSS and cornual hematometra. And as far as
8 ablation and cancer, gynecologic cancer is the
9 most common of all -- or endometrial cancer is
10 the most common gynecologic cancer, but the
11 death rate isn't that high, because we usually
12 can diagnose it with post-menopausal bleeding.

13 Our concern is that if you obstruct
14 that bleeding, you might delay the diagnosis.

15 And this was the first asymptomatic
16 endometrial cancer case that was published.
17 And Baggish and Valle state that endometrial
18 ablation should not be performed as a means of
19 eliminating post-menopausal bleeding, since
20 the risk of masking and delaying the diagnosis
21 of cancer far outweigh any benefit accrued by
22 the cessation of bleeding.

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1 And it's really too early to know
2 if endometrial cancer after an ablation will
3 be problematic, because the mean age for
4 endometrial ablations is 40.5. The mean age
5 for cancer is 64.4. So we are talking about
6 almost 24 years. And ablations became popular
7 in the mid-'90s, so we're only out about 12
8 years. We're going to have to have another 12
9 years before we're going to find out how much
10 of a problem this is.

11 So I believe the consent form
12 should include not only short-term, but also
13 the long-term complications and the delay. The
14 patient needs to know that the delay in the
15 diagnosis -- I'm sorry. The procedure itself
16 may put the patient at risk for additional
17 surgery, including a hysterectomy, to correct
18 these long-term problems.

19 And this is my last thing to say.
20 In the green journal that just came out, just
21 last week, there was a randomized control
22 trial study looking at hysterectomy versus

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1 endometrial ablation. And the endometrial
2 ablations were equally divided between
3 resectoscopic and non-resectoscopic.

4 And they found that one-third of
5 the -- almost one-third of the patients who
6 had an ablation ended up with a hysterectomy
7 if you followed them for five years. And
8 almost all of these were due to pain. So I
9 think it's critical in any patient who is
10 having a cosmetic ablation, she has to know
11 that the procedure itself may be setting her
12 up for a future hysterectomy. Thank you.

13 CHAIR CEDARS: Thank you. And the
14 next speaker is Dr. Ellen Sheets.

15 DR. SHEETS: Thank you. Good
16 morning, Madam Chair and Members of the Panel,
17 ladies and guests. I'm Dr. Ellen Sheets,
18 Chief Medical Officer, Senior Vice President
19 of Hologic, Inc., who markets the NovaSure
20 device for endometrial ablation. On behalf of
21 the company, I would like to thank Mr. Pollard
22 and the FDA for the opportunity to address

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1 this Panel with questions that we have
2 regarding the clinical research approach
3 accompanied with follow-up to obtain FDA
4 approval to market an endometrial ablation
5 device for the purpose of electively
6 eliminating or significantly reducing a
7 woman's normal menstrual flow.

8 I would also like to thank the FDA
9 for presenting the issue of using endometrial
10 ablation for the cessation of menses to this
11 Panel.

12 Women have already chosen to
13 suppress their menses. We know from peer
14 review published surveys that premenopausal
15 women that 50 percent or greater would prefer
16 to have amenorrhea. And in fact, over 75
17 percent of menstruating women have indicated
18 that menses interferes with their sexual life
19 and over 28 percent have indicated that menses
20 interfered with their work life and would like
21 at least a reduction in menstrual frequency.

22 Hence, new formulations of oral

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1 contraceptives for extended suppression of
2 menses and hormone eluting IUDs that also
3 suppress menstruation have come to market.
4 Women use these methods of menstrual
5 suppression despite side effects, breakthrough
6 bleeding and the potential for long-term
7 health concerns.

8 We would pose that for women who
9 have completed childbearing and are committed
10 to permanent birth control they should have
11 the option to elect the permanent solution to
12 menstrual cessation, which we believe would be
13 best offered by allowing these women elective
14 access to endometrial ablation.

15 When Hologic discusses the
16 possibility of an elected use clinical trial
17 in this arena, three areas of concern
18 consistently come to light. We believe these
19 concerns are consistent with those of the FDA
20 and wish to express to this Panel the
21 importance of providing guidance in these
22 areas.

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1 First is the issue of how to ensure
2 that women being considered for cessation of
3 normal menses actually are experiencing normal
4 menstrual flow. Second is to understand to
5 what extent it is necessary to document
6 quality of life changes after treatment to
7 abate normal menses. And finally, how to
8 measure success in a proposed trial, given
9 that women have already accepted some
10 breakthrough bleeding while using the
11 currently available methods for menstrual
12 suppression.

13 It would seem that identifying
14 women with normal menses should be fairly
15 straightforward, but as we know, women often
16 under or overestimate their menstrual flow.
17 Given that these sanitary products that were
18 validated for PBLAC are no longer commercially
19 available, we feel that the Panel should
20 consider other techniques to identify normal
21 menstruating women, such as menstrual diaries.

22 Although one would assume that

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1 PBLAC could be continued with a simple
2 revalidation exercise, the super absorbency of
3 current sanitary products will likely require
4 further modifications to the Higham scoring
5 system.

6 Additionally, the scoring system
7 that was originally developed was primarily
8 designed to identify menorrhagia not normal
9 menses. Thus, we would contend that if
10 utilized, the intent of PBLAC score should be
11 changed to simply rule out those women with
12 abnormal menses by eliminating women with high
13 scores, such as that equal to 100 or greater
14 of the old Higham classification.

15 Any attempts to stratify a women's
16 menses below that mark we believe would be
17 difficult, if not impossible to accurately
18 validate.

19 In regards to quality of life, I
20 fully disclose I am no expert. However, a
21 PubMed search leaves one hard pressed to find
22 a review of quality of life instruments used

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1 in what are apparently normal patients.
2 Although women would seek cessation of their
3 normal menses might not have completely normal
4 quality of life, they are certainly not
5 individuals for whom it would be expected to
6 see a dramatic increase in quality of life
7 just because their period was eliminated or
8 reduced.

9 It would seem the quality of life
10 instruments are best utilized in a before and
11 after comparison in patients who are being
12 treated for an abnormality or disease entity.
13 In prior NovaSure studies, we have used a
14 simple general descriptive measure to gather
15 information about a patient's satisfaction
16 with the procedure.

17 In these cases, we evaluate the
18 level of satisfaction that patient's perceived
19 after the ablation for abnormal uterine
20 bleeding and we believe that such simple
21 descriptive information gathering would be
22 very appropriate in the proposed setting of

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1 cessation of menses as well.

2 Given that women already accept
3 breakthrough bleeding when using hormonal
4 suppression of menses, what should be the
5 measure of success when a permanent treatment
6 to eliminate menses is utilized?

7 Women have told us that simply
8 reducing their menstrual flow along with
9 decreasing the frequency of bleeding is
10 important to them. While some might believe
11 that amenorrhea would be ideal, we would
12 contend that a combination of oligo and
13 amenorrhea is the best acceptable endpoint.

14 Additionally, with oligomenorrhea,
15 we would expect that the timing of such
16 spotting, if it were to occur, might be
17 unpredictable for some women, given that for
18 some, not every month, would they have regular
19 cyclic bleeding.

20 The post-treatment documentation of
21 cessation of suppression of menses again the
22 question arises as to the validity of PBLAC in

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1 determining safety and effectiveness and
2 significantly reducing bleeding levels. We
3 would suggest considering use of a menstrual
4 diary with defined parameters to document
5 amenorrhea or oligomenorrhea. Such a diary
6 could be adapted from work done for hormonal
7 suppression of menses related to extended use
8 of a combination of oral contraceptives or
9 medical treatment of uterine fibroids.

10 Here is an example of a menstrual
11 diary approach utilized in pharmaceutical
12 studies and one that could be used to
13 determine safety and effectiveness in an
14 elected endometrial ablation study. It would
15 seem that in addition to amenorrhea a small
16 number of episodes per month of Level 1
17 spotting could be -- should be an acceptable
18 endpoint for normally menstruating women after
19 endometrial ablation.

20 In summary, allowing women more
21 choices in managing their menstruations, seems
22 essential given what women are telling medical

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1 professionals today. It is important to
2 develop a least burdensome approach to
3 providing these choices in an expeditious
4 manner that involves an active dialogue
5 between FDA and industry to provide guidance
6 on labeling and clinical data necessary to
7 assure patient safety and effectiveness.

8 We again thank the FDA for bringing
9 this matter to the Panel's attention and look
10 forward to the discussion ahead. Thank you.

11 CHAIR CEDARS: Thank you. Is there
12 anyone else from the audience who would like
13 to address the Panel, at this time? If you
14 would, please, give your name and any
15 affiliation?

16 DR. STABINSKY: I'm Dr. Seth
17 Stabinsky. I'm a private practitioner in San
18 Jose, California and I specialize in
19 hysteroscopic surgery. And I have no
20 affiliation for anything that is being
21 discussed today.

22 First, I want to make a public

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1 statement. Then I want to thank Dr. Arthur
2 McCausland for being the professorial person
3 that he is and coming here and giving an
4 incredibly powerful talk just now about the
5 concerns that we should have about endometrial
6 ablation and also his comments yesterday. And
7 I think he came here on his own dime and just
8 out of a desire to take care of women that are
9 out there and make sure that we protect them
10 and I think that's pretty impressive.

11 But I also would like to raise a
12 question to really throw a monkey wrench into
13 your discussions. And that's that as a
14 clinical practitioner, one of the issues that
15 has become or that I'm struggling with is the
16 patient comes to me with menorrhagia and
17 potentially needs a sterilization as well, who
18 wants an ablation. We have a quagmire and a
19 difficulty now in having to wait three months
20 to do an HSG on that patient for the
21 sterilization -- for sterilization purposes
22 and yet she has come to us for bleeding. So

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1 we have to tell someone who is bleeding really
2 heavily to wait three months.

3 So I think there is a question out
4 there that, to me, I would like to see get
5 answered as a clinician. And that's what
6 about the combined hysteroscopic sterilization
7 techniques and endometrial ablation together
8 and their effect on fertility?

9 We know that people can get
10 pregnant after endometrial ablation and we
11 know that they can get pregnant after
12 sterilization. We saw that yesterday. But
13 the combined technique, is there a chance that
14 that reduces fertility so much that it no
15 longer becomes a concern? There are a bunch of
16 other concerns that Dr. McCausland raised, but
17 by combining endometrial ablation and
18 sterilization, do we reduce those risks enough
19 that that might be the patient population we
20 should be looking at for a study of what you
21 are sort of looking at.

22 One of the principles of ethics

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1 that was discussed earlier is beneficence and
2 if we were to approach patients who were
3 interested in sterilization and had normal
4 menses and had described the kinds of things
5 that Dr. McCausland pointed out and the need
6 for a consent form and those patients wanted
7 to go ahead, is there a possibility of being
8 able to do concomitant endometrial ablation
9 and hysteroscopic sterilization and then
10 follow those patients in an appropriate manner
11 and not wind up having to do an HSG on those
12 patients down the road?

13 I know he put up a slide that
14 showed a picture of Essure along with a
15 hysteroscopic - - Essure and NovaSure
16 procedure and he put up a picture that showed
17 open tubes afterwards. I'm not sure what the
18 background of that was, but I think that's a
19 question that needs to be answered for the --
20 as these become much more prevalent out there.

21 If we do a sterilization and we do
22 an ablation at the same time, do they really

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1 need a hysterosalpingogram? And what are the
2 risks involved for the patient of actually
3 getting pregnant afterwards? So I hope the
4 Panel will throw that into their discussions
5 and I'm very much looking forward to hearing
6 what you have to say.

7 CHAIR CEDARS: Thank you.

8 DR. STABINSKY: Thank you.

9 CHAIR CEDARS: Is anyone else
10 interested in speaking with the Panel? Again,
11 please, state your name and affiliation.

12 MR. SLOAN: Good morning. My name
13 is Todd Sloan. I'm the Director of Marketing
14 for Boston Scientific in the Women's Health
15 Division. We market the HGA system, which is
16 an endometrial ablation device. And first, I
17 would like to say we appreciate the FDA's
18 comments earlier today and agree, you know,
19 with the issues of efficacy, risks and benefit
20 analysis, counseling, business ethics, the
21 medical ethics that were all highlighted by
22 the FDA.

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1 I would like to bring up one other
2 perspective and that is that menorrhagia today
3 has a broad definition. In the clinical
4 trials, we have used really the monthly flow
5 of greater than 80 milliliters per month.
6 However, menorrhagia in the real world is
7 defined more broadly. It could be atypical
8 frequency, atypical length and
9 unpredictability in addition to just excessive
10 flow.

11 And today, the diagnosis of
12 menorrhagia and the subsequent treatment is a
13 collaborative process between the patient and
14 the physician, which we feel, you know,
15 results in high satisfaction levels today for
16 both the patient and the physician.

17 In the process of designing trials
18 for the "normal" patient population, we may
19 be, in fact, defining abnormal. And it is
20 potentially concerning to us that if we simply
21 use flow rate to define normalcy, then we will
22 be defining menorrhagia simply as excessive

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1 flow.

2 And I ask that, you know, as we
3 design and define inclusion criteria for the
4 clinical trials that clearly require some sort
5 of an objective definition and view of
6 outcomes, that we use caution that we don't --
7 that we maintain a broad and subjective
8 definition for menorrhagia broadly, so that
9 patients and physicians continue to have
10 access to the numerous treatment options
11 available today, without prerequisite testing
12 or other methods to force objectivity into the
13 real world clinical setting, which is today
14 subjective and working well. Thank you.

15 CHAIR CEDARS: Thank you. Is there
16 anyone else who would be interested in
17 addressing the Panel, at this time? If not,
18 we will proceed with the discussion of the FDA
19 questions. If we can have the first question
20 up on a slide? For those Panel Members, these
21 questions were in your pamphlet. Please, note
22 there is a change from what was sent out

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1 earlier and there is a new Question No. 1.

2 While they are pulling up that
3 first slide, the first question had to do with
4 the ethical principles and we had a very nice
5 introduction of that this morning by Ms.
6 Price. And I think it's important to begin
7 the discussion by asking if these ethical
8 principles, particularly autonomy and
9 beneficence or non- maleficence, are relevant
10 to a trial that would have to do with elective
11 uterine ablation techniques for cessation of
12 menses.

13 I would like to open that up to the
14 Panel. Dr. Romero?

15 DR. ROMERO: I think I would be
16 interested if anyone can comment with regard
17 to how those principles, to their knowledge,
18 have been applied in the realm of other
19 elective procedures, cosmetic surgeries, not
20 gynecologically-related. But my sense is that
21 that would be very helpful for us to then
22 consider these questions.

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1 CHAIR CEDARS: Does anyone from the
2 FDA have experience with how these principles
3 have been applied to cosmetic surgery?
4 Because that's not something typically in
5 obstetrics and gynecology.

6 MS. BROGDON: Personally, I can't
7 think of any cases where they have been
8 applied in an intentional manner. For
9 instance, for refractive surgery in
10 ophthalmics, that has kind of been incorporated
11 into the discussions, but not discussed
12 separately. I'll ask any of the other FDA
13 attendees if they can think of any other
14 situations. No, we can't.

15 CHAIR CEDARS: Dr. Romero?

16 DR. ROMERO: Yes, the reason why I
17 asked that is because I know it was suggested
18 that what is before us today be likened to
19 breast augmentation. And, you know, my sense
20 is that this is much more complex given, from
21 my understanding, the potential for adverse
22 effects and particularly serious adverse

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1 events associated with endometrial ablation.

2 So I guess what I'm struggling with
3 from the perspective that I am supposed to
4 bring here, with whether this is the
5 situation, for instance, that the FDA -- what
6 exactly is the position of the FDA when being
7 presented with a potential for an application
8 for a product that is not medically necessary?

9 I just feel that that's necessary.

10 CHAIR CEDARS: Ms. Brogdon?

11 MS. BROGDON: May I say that's why
12 we're having this discussion.

13 CHAIR CEDARS: If I can maybe start
14 the discussion? If I think in terms of
15 relevance to this particular topic and may or
16 may not be parallel with other cosmetic
17 surgery, but I think the issue of autonomy and
18 it was raised by one of the public speakers as
19 well as by Veronica Price, the issue of
20 autonomy in terms of a patient's ability to
21 make a decision about their choices for
22 menstrual bleeding.

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1 And so, one, the difference between
2 sort of autonomy and when does it potentially
3 become paternalistic to either allow or
4 disallow or require, because there were issues
5 about military personnel, and then secondly,
6 do the issues of autonomy for elective
7 procedures shift the risk/benefit ratio?

8 So perhaps if we could discuss
9 those issues? Dr. Ramin?

10 DR. RAMIN: I was just going to say
11 that in obstetrics, we do have some experience
12 over the last year and a half with patient
13 choice cesarean delivery. So it's not the use
14 of a device, but it is the concept of the
15 ethics of autonomy where a patient being
16 informed of the risks and the benefits can
17 make the decision to have an elective cesarean
18 delivery. So we do have that experience.

19 CHAIR CEDARS: And can you share
20 how that has -- how you have been balancing
21 those risks and benefits in obstetrics?

22 DR. RAMIN: Certainly. I mean,

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1 basically, we have to explain and fully inform
2 the patient the risks of anesthesia, the risks
3 of an operative procedure and then also
4 discuss the benefits potentially, again, of
5 pelvic floor dysfunction. Some patients
6 choose not to want to labor or have the pain
7 of labor and after the patient has been
8 informed, consent signed, then it's up to the
9 physician if they individually would proceed
10 with agreeing with what the patient's choice
11 is.

12 CHAIR CEDARS: Dr. Stubblefield,
13 was your point directly on point to this or
14 can I come back to that?

15 DR. STUBBLEFIELD: You can come
16 back.

17 CHAIR CEDARS: Okay. Dr. Peterson?

18 DR. PETERSON: You know, I think
19 that's very helpful, because we do -- we are
20 facing dilemmas that are helpful in framing
21 this out in the specialty. And I think one
22 issue about the ethical considerations is the

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1 ethical issues around the indication per se
2 and the practices per se and the others, the
3 ethical implications for any trial design that
4 would lead to a potential indication.

5 And most of us have been on ACOG
6 Practice Committees or Bulletin Committees or
7 Committee Opinions and when I was trying to
8 frame this out, because it is so complicated,
9 I was thinking all right, so we're in the room
10 and the issue in terms of what is desired is
11 cessation of menses in a woman who has normal
12 menses, but is completed with childbearing.

13 And so that's the question to the
14 GYN Practice Committee for the bulletins. And
15 say well, how about hysterectomy? Let's say
16 it's okay to do a hysterectomy in this
17 situation, based on autonomy, well, most
18 people in the room would say you've got to be
19 kidding. You know, I mean, it would be a show
20 stopper right there. And the reason would be
21 you don't do a hysterectomy in a woman with no
22 pathology or you don't do a -- and so most

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1 people at that point would say look, the risks
2 of that procedure are way too great to be
3 doing it for that indication.

4 And so to me, in framing it out, if
5 that were true, let's just assume for
6 discussion it would be true, then the only
7 reason to think about endometrial ablation as
8 an alternative to hysterectomy, as it has been
9 for a disorder, would be that it is so safe
10 that it's fine. You know, I mean, it's just
11 an informed consent issue. I mean, there are
12 certain risks and benefits and everything, but
13 that it's so safe that it's okay to look at
14 this as an issue of patient choice.

15 And so I think if we're approaching
16 it that way, then the burden then starts to
17 shift and the bar starts to look pretty high
18 in terms of what is safe. So as Dr.
19 McCausland said, there is some potential
20 long-term safety issues. There is this
21 short-term perioperative safety issue. And as
22 somebody else said, there is the permanent

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1 issue.

2 I mean, I think one of the most
3 outstanding things we spent a couple of
4 decades studying sterilization and one of the
5 biggest surprises was the rate of regret.
6 People were absolutely dead solid certain that
7 they didn't want any more children, but in the
8 19 to 24 year-old age group, 40 percent later
9 requested information about reversal.

10 So when we start saying well, it's
11 so safe, then it would appear that there is a
12 substantial burden to demonstrate that safety,
13 so that it then becomes a matter of choice,
14 because it's not a matter of choice right now
15 for hysterectomy. But we are saying is this
16 so much safer that it's a matter of choice for
17 this?

18 And it's unusual. I think part of
19 the earlier discussion about a departure is
20 that hysterectomy is a procedure. Well, this
21 is a device, but it's also a procedure. And
22 it's that link that is even causing us to

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1 raise the question.

2 CHAIR CEDARS: Thank you for that
3 nice summary. Dr. Sharp? Okay. Any other
4 discussion about this point before we go to
5 Dr. Stubblefield?

6 DR. STUBBLEFIELD: Now, this is
7 related to that point. It's not separate. I
8 just wanted to say that in considering the
9 principles of ethical decision making, you
10 don't just spend all your time on autonomy.
11 And no one of these four rates being
12 considered more highly than the other. It's
13 the balance of taking the whole picture.

14 And just to put it in that context,
15 what Bert has been talking about, there is a
16 big burden here when it comes to
17 non-maleficence. I'm very concerned when --
18 from what I read before I came and what I
19 heard presented by Mr. McCausland that we
20 don't know yet how big that burden is.

21 It sounds like it's large. And we
22 have a backlog of women that have had

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1 endometrial ablation for the last decade who
2 are just now beginning to realize how many
3 potential problems and real problems there
4 are. And I think it would be really premature
5 to extend the indication and find out 5 or 10
6 years from now that we have a major national
7 health problem that we caused.

8 CHAIR CEDARS: Thank you. Dr.
9 Hillard?

10 DR. HILLARD: Just to speak very
11 briefly on the issue of autonomy and to raise
12 an issue that goes beyond that, but as we
13 think about women making a decision if this
14 were to be an option, we assume an informed
15 decision. And I worry about the ability, our
16 ability and women's understanding of this
17 choice.

18 And I think that as many women
19 think about their menstrual periods, they
20 think about not only the bleeding per se, but
21 they think about other symptoms and other
22 experiences that go along with it. And so if

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1 one looks at some of the other literature
2 around women's choices of frequency of
3 menstrual periods, there are a whole variety
4 of menstrual molimina, menstrual symptoms that
5 women lump into that category that relates to
6 their period.

7 So if you asked the question how
8 often do you want to have your period, women
9 also put in there the experience of cramps or
10 dysmenorrhea, breast tenderness, headaches,
11 the whole experience of their menstrual
12 period. So one of the concerns that I have as
13 we discuss this is that women might be
14 choosing to ablate their endometrium and not
15 then being successful in getting rid of these
16 other menstrual, premenstrual molimina that
17 are not due to bleeding per se, but that are
18 hormonally related.

19 And so I think that that's another
20 layer, another complicating factor that we
21 need to at least raise and bring out along
22 this issue.

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1 CHAIR CEDARS: Absolutely. Dr.
2 Romero?

3 DR. ROMERO: Two comments.
4 Particularly following up on Dr. Hillard's
5 point is, I think, it will be part of another
6 question we consider, but what it pertains to
7 is the kind of data that potentially would be
8 collected, these quality of life, for
9 instance, measures that have been spoken of,
10 and I think that makes a very strong argument
11 if we were to proceed down this path, that
12 data be collected pre- and post-surgical
13 procedure, because I think getting at the crux
14 of measuring any kind of endpoints or effect
15 would be exactly what the patient desired in
16 the first place. And what informed that demand
17 or desire?

18 So I would very strongly disagree
19 with one of the speakers who suggested that
20 only data, very simple, and I'm not sure what
21 that means, but very simple quality of life
22 data be collected after the treatment. So I

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1 don't digress, but I think that it pertains to
2 that point.

3 On this issue of ethics though, I
4 think another thought that I have would be
5 probably more pertaining to autonomy, but not
6 wanting to give that component of this ethical
7 discussion more weight, is exactly what is the
8 -- where is potentially the demand or need for
9 this type of procedure coming from?

10 And the way I see it, minimally, is
11 that there is the sort of commercial interests
12 that, you know, have some say or, you know,
13 desire in this. There might also be sort of a
14 statement of consensus, some kind of
15 discussion around medical need and that would
16 clearly come from the medical community and
17 then sort of from the patient or consumer
18 side.

19 And what has been spoken to is that
20 these products exist and they have the
21 potential for doing this and some presumption,
22 I think, of or statements around the patient

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1 or client desire, but, you know, I think this
2 sort of where, if and where, medical need or
3 recommendation is an -- important in a missing
4 area.

5 Around I think a lot is being -- a
6 lot of discussion around patient desire,
7 women's desires is being discussed. And I
8 think from the data that we have been
9 presented with, that that is potentially
10 biased toward more educated women, toward
11 caucasian women and possibly -- well, not only
12 in this country, but I think that that's a big
13 missing piece where women with different
14 demographic characteristics and cultural
15 backgrounds come into play.

16 And once that is considered this
17 notion of desire, demand might change
18 dramatically.

19 CHAIR CEDARS: Thank you. Dr.
20 Sharp?

21 DR. SHARP: I am just struggling a
22 little bit with the definition of normal,

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1 because really if someone is coming to you and
2 saying I'm bothered, my lifestyle is being
3 bothered by this, to me that may not be
4 normal. And I wonder if this isn't already
5 happening all the time, every week, every day
6 in the U.S.

7 Someone comes in, they are having
8 some bleeding, it's bothersome to them. It
9 may not have to be exactly seven days. They
10 may not have to have anemia, but maybe it's
11 heavy to them and a hysterectomy is done or
12 endometrial ablation is done. We know that
13 the PBLAC scores in a lot of women who came in
14 with -- in these trials that said hey, I have
15 this really heavy menses and their PBLAC
16 scores were less than 75.

17 So I wonder is this really just
18 asking the FDA for a stamp of approval to do
19 this on anyone who wants it or are we really
20 trying to define is there an abnormal -- is
21 there a patient -- is it more of a patient
22 issue where they are bothered by it?

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1 And I would think that would really
2 fall more to the individual patient/ physician
3 relationship, because if you've got here -- a
4 minute ago, you had psychiatric evaluation. I
5 would think that that might be difficult in
6 and of itself, because if someone comes back
7 and they have a common diagnosis of depression
8 or something, which is going to be high,
9 because it's high in the population, then do
10 you not do that?

11 So I struggle with the definition
12 of normal. And I just wonder if this isn't
13 already something that is happening anyway and
14 we're just looking for a stamp of approval.

15 CHAIR CEDARS: I think the FDA may
16 want to address that.

17 MR. POLLARD: Yes, let me just sort
18 of provide a little perspective, because I
19 want to sort of separate the issue of practice
20 of medicine, which I think is really where you
21 are coming from primarily, and I think it's
22 where the practice bulletin comes from. The

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1 question FDA is posing to you is a little bit
2 more structured within the regulatory
3 framework of regulated medical device and an
4 approved indication for use on the labeling
5 and the ability to promote a product.

6 So it is a narrower framework for
7 looking at that question. And I wouldn't
8 disagree, but there may be docs all over the
9 country that interact with their patients and
10 based on that interaction, decide to, you
11 know, offer the patient endometrial ablation.
12 But what we are really asking the Panel is to
13 help us look at the question when we've got
14 these approved products out there for one
15 indication and that company then wants to
16 study that device and possibly, in the future,
17 market that device for that indication.

18 How should we go about guiding them
19 in that context? So that's one point. And
20 then just secondly, while you are on Question
21 No. 1, and I'm glad you mentioned the second
22 half of that, we would be interested in

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1 Panel's input on some of those proposals that
2 have been suggested to us as other possible
3 means of making sure patients understand what
4 they are getting into.

5 CHAIR CEDARS: Thank you. I'm
6 going to hold your question, I think, because
7 I think Ms. George wants to address this
8 particular issue.

9 MS. GEORGE: I just want to
10 re-voice what Colin said. It's that as
11 industry, one of the things that we are
12 obligated to do is kind of monitor how doctors
13 are using our medical devices. And if we see
14 you doing things outside of that, first, we
15 are supposed to try to tell you shame on you,
16 you shouldn't be doing that. And then if we
17 see it happening prolifically, we're supposed
18 to go to the FDA to try to start going through
19 that approval process.

20 So I think not that I want to see
21 us go and get rid of some of the flexibility
22 that the Boston Scientific gentleman

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1 mentioned, but I think if this is prolific and
2 happening without adequate controls and
3 approvals, then that's why the FDA is kind of
4 asking us to help them come up with the best
5 way to do this to separate guidelines.

6 CHAIR CEDARS: Thank you. Dr.
7 Sharts-Hopko?

8 DR. SHARTS-HOPKO: Yes, a part of
9 this that keeps me stuck is that I don't think
10 we can operationally define the concept of in
11 whom childbearing is completed. We have so
12 much history about seeking reversals of
13 permanent procedures. We know socially our
14 divorce rate is at 50 percent. We know that
15 people are overriding natural menopause to
16 have children.

17 I mean, if you look at the whole
18 assisted reproductive technology realm, it
19 lends some question to that idea.

20 CHAIR CEDARS: So, Dr. Peterson?

21 DR. PETERSON: Just if we could
22 follow-up on the FDA's point. I think it's

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1 helpful. We're trying to look at trial
2 designs to demonstrate that an indication is
3 an appropriate indication. And some of what
4 you just touched on, I think, may be helpful
5 to explore.

6 What does an indication mean? It
7 has been more straightforward for us with the
8 sterilization techniques and somebody desires
9 permanent contraception. And then we're
10 looking at trying to help you decide whether
11 or not a bar has been met or not met with
12 respect to safety and effectiveness.

13 But in an indication for what would
14 otherwise be considered a normal situation and
15 whether or not it is okay to do a surgical
16 procedure for that, what does an indication
17 mean?

18 MS. BROGDON: If we approved in a
19 marketing application an indication such as
20 this, it would be saying FDA had found the
21 device used under those circumstances to be
22 safe and effective. And the sponsors could

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1 advertise their device as being approved for
2 that purpose.

3 So we are asking you how would
4 devices need to be studied in order eventually
5 to get approval for those sorts of
6 indications?

7 CHAIR CEDARS: And I think we will
8 be discussing the specific outcome and that
9 may relate to this a bit as well. Dr. Davis?

10 DR. DAVIS: I think as I look at
11 this, of course, autonomy is always extremely
12 important to all of us that do women's health
13 care. But to me, one of the risks revolves
14 around this regret in the small subset of
15 women who actually may be encouraged by
16 employers, such as the military and military
17 situations, to have this done.

18 I see that as a risk. And then
19 comes up the justice and the non-maleficence
20 really becomes very important and that's a
21 risk that we wouldn't usually think of as part
22 of the procedure.

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1 I also would like to say for the
2 second part of this question, I would have
3 some serious reservations of just using
4 counseling sessions and second clinical
5 opinions. And I think if I could be so bold
6 to say so, we can look to this elective
7 C-section and perhaps Susan can comment on
8 this, that seldom are you going to send
9 someone to the other clinician who disagrees
10 with you if you are willing to do it.

11 And there is that tendency, so I'm
12 just worried that the counselor would really
13 have to be someone that would definitely
14 support and provide data on both sides of the
15 question equally, which is difficult to
16 legislate.

17 CHAIR CEDARS: Dr. Stubblefield?

18 DR. STUBBLEFIELD: I would like to
19 ask about another complexity here and that is
20 pregnancy. These are sexually active women,
21 most of them, and they are still fertile, most
22 of them, and we seem to have considerable

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1 concerns about tubal sterilization in
2 combination with endometrial ablation.

3 I don't see how you can separate
4 contraception discussion and issues from the
5 endometrial ablation issue. You've got to
6 think about the whole picture or we're doing
7 our patients a big disservice. We can't be
8 like the general surgeons used to be in
9 treating with a pregnant woman with breast
10 cancer and just say well, go get rid of the
11 pregnancy and I'll come talk to you about your
12 breast cancer.

13 We're beyond that. We've got to
14 look at the whole picture. And that -- I'm
15 just thinking of one example in medicine with
16 the -- I'm blanking on the name of the drug
17 that is used to treat asthma -- acne when all
18 else has failed.

19 CHAIR CEDARS: Accutane.

20 DR. STUBBLEFIELD: Accutane, which
21 is a serious teratogen, and as a result the
22 FDA has specified, I believe, that women have

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1 to be on two means for birth control, if they
2 are going to be on that drug. So there is a
3 case where the FDA has gone on to specifically
4 deal with the issue.

5 Are our concerns about pregnancy
6 after endometrial ablation big enough that we
7 should have that kind of a warning? I don't
8 know, but I want to raise the issue.

9 CHAIR CEDARS: Okay. I think that
10 raises a really good point and that gets into
11 one of the later discussion questions about
12 tubal sterilization or permanent
13 sterilization. It also gets into the issue, I
14 think, if the FDA doesn't mind if we blur
15 things a little bit, but it gets into the
16 issue a little bit in terms of a control
17 group, which is kind of the next part as we
18 start to talk about a study design.

19 And as the FDA mentioned, there are
20 no other drugs or devices approved for this
21 indication. But if, in fact, you need some
22 kind of contraception along with this

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1 technique, then, you know, would you be able
2 to have a comparator that was something that
3 was contraceptive as well as induces
4 amenorrhea?

5 So since that's kind of the next
6 question in terms of can there be a control
7 group? It seemed as though the FDA's
8 presentation this morning felt as though there
9 could not, so what's the sense about whether
10 or not there can be a control group? And then
11 if not, what kind of targeted endpoint are you
12 going to have? Dr. Gilliam?

13 DR. GILLIAM: I feel like a broken
14 record, but I think it's very important to
15 have a control group and a study like this.
16 Women need to know this product works so well
17 compared to what? My candidate would be a
18 Levonorgestrel intrauterine device. Here you
19 would have a woman would be able to day I have
20 this amount of amenorrhea by this reversible
21 easily placed, easily removed device that also
22 gives me contraception and amenorrhea versus

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1 this procedure.

2 CHAIR CEDARS: Dr. Propert?

3 DR. PROPERT: I realize this isn't
4 the order of the questions here, but I think
5 it's premature to talk about a control group
6 before we talk about the endpoint, because to
7 me the endpoint is going to drive the control
8 groups. I realize that's backwards from the
9 questions, but in order for me to even think
10 about the control group, I need to know what
11 we are going to be measuring, whether it is
12 patient satisfaction, amenorrhea or whatever.

13 CHAIR CEDARS: Dr. Sharp?

14 DR. SHARP: I was going to say the
15 one thing that would be interesting about
16 looking at patients over time, because there
17 are real issues with patients who are not
18 sterilized who then become pregnant, for any
19 of you who have cared for those women, it's
20 tough. It's a difficult situation to care for
21 someone who has had an ablation, who has
22 become pregnant versus the group that might

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1 have been sterilized and have all the things
2 that Dr. McCausland talked about.

3 So I think one of the interesting
4 things of a single arm study is it may enable
5 you to look at both those groups when you are
6 done. Certainly suggesting that they have some
7 form of birth control, but -- or
8 contraception, but know that they may not be
9 compliant or may have failure. So that would
10 be the one advantage of being able to look at
11 that as a secondary endpoint.

12 CHAIR CEDARS: I think I get the
13 sense from the way it was presented by the FDA
14 that the endpoint, although it's not a
15 specific endpoint, is the elective cessation
16 of menses. I think the specific endpoint
17 whether that's complete amenorrhea or whether
18 that is amenorrhea plus spotting is, I think,
19 the question that comes up later. But I think
20 the global goal is an elective cessation of
21 menses. So not a correction of the pathologic
22 menorrhagia, but an elective cessation of

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1 menses.

2 And so the question is given that
3 there is no other approved product for that
4 same indication, can you design a study that
5 has a control group or does that need to be a
6 single arm study? Dr. Propert?

7 DR. PROPERT: I mean, I realize I'm
8 coming from a different group here. But is it
9 decided that that's the appropriate endpoint
10 in a group of people like this? This is going
11 to sound a bit off the wall, but why isn't
12 whether the patient is happy with having had
13 the procedure really what you want to ask?
14 Especially given your comments about all of
15 the other things that go along with
16 menstruation that are not going to be improved
17 by this procedure?

18 CHAIR CEDARS: Ms. Brogdon?

19 MS. BROGDON: Dr. Sharp, I don't
20 think the staff completely understood the last
21 point that you made. Could you go through
22 that again, please?

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1 DR. SHARP: Sure. So if you were
2 doing a single arm study and we've just heard
3 quite a number of issues that Dr. McCausland
4 has brought up with the PATSS syndrome and
5 etcetera. And also, there is the risk of
6 those who -- so there is an argument for, you
7 know, should everybody be sterilized if you
8 are going to put them in a trial?

9 You have also got this other group
10 that, you know, if they are not sterilized,
11 don't have a tubal blockage, then they are
12 less likely to get PATSS syndrome. What
13 impact does that have? What impact does
14 ablating a lot of women with -- for elected
15 reasons? What is the effect? What -- if you
16 look at the group that was sterilized and the
17 group that was not, so you didn't necessarily
18 have that as an inclusion criteria, but you
19 look at that post- hoc.

20 MS. BROGDON: As an outcome.

21 DR. SHARP: As an outcome, as a
22 secondary outcome. Is that more clear?

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1 CHAIR CEDARS: Dr. Peterson?

2 DR. PETERSON: The -- I think part
3 of the difficulty we are having is trying to
4 use a study to demonstrate an outcome that
5 would necessarily require a comparison group.

6 And if we're looking at safe and effective,
7 it's virtually always compared to what.

8 The difficulty is that from the
9 standpoint of practice in trying to create a
10 new practice that doesn't exist currently, it
11 would be well, if you are saying it's okay to
12 do this, it would be potentially compared to
13 like an IUD or oral contraceptives or some
14 other way to address the clinical non-issue or
15 issue, depending on how you look at it.

16 So I think one is an epidemiologic
17 issue and the other is sort of a clinical
18 practice issue, because ultimately when you
19 try to use the findings of those studies, it
20 is going to be okay, we've demonstrated this
21 as safe and effective relative to that or we
22 have demonstrated the fundamental question,

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1 which is is this really safe enough in the
2 short and the long-term to say it's okay to
3 have as a patient choice?

4 And they are two separate issues
5 and they require different designs. I think
6 if we go back to where we were in the '60s
7 with the pill being first approved in 1960,
8 there was a great deal of angst about this,
9 you know, incredible new potential for good.
10 And we don't really know how safe this is. So
11 many studies were launched to look at short-
12 term and long-term issues that we now know
13 more about the pill than any other drug in the
14 pharmacopeia.

15 But it was -- that duty owed was
16 felt, because these are largely normal healthy
17 people. It's not, you know, a health problem
18 that we're trying to fix. And to me, that
19 duty owed rings some resonate cord with a
20 situation like this. I mean, we have heard in
21 the last 10 or 15 minutes just a series of
22 potential serious long-term health effect

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1 issues about pregnancy after endometrial
2 ablation, issues about endometrial ablation
3 and sterilization syndrome, etcetera,
4 etcetera.

5 The risk of regret in the people
6 who had this. You know, we're talking about
7 35 and older, but we also said well, maybe
8 that's not what the cutoff is going to be.
9 Maybe we're talking about younger people and
10 these issues of regret. So there are so many
11 potential issues about is this safe that a
12 study would potentially have to address, that
13 there is -- you know, I mean, it seems to me
14 that we are talking about studies that are
15 long-term, involve a large number of people,
16 very expensive to do. The bar seems to be
17 pretty high to me.

18 CHAIR CEDARS: I just want to tell
19 you, we do have several other questions to
20 move on to. Does anyone have any specific
21 questions or comments about the second half of
22 Question 1? And I think looking at this, we

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1 should also put it in the context of the
2 discussion yesterday, in terms of if you
3 required something for the clinical trial,
4 would that then be required for putting it
5 into clinical practice and that gets a bit to
6 what Dr. Davis was talking about a minute ago.

7 Ms. Brogdon, do you have enough for
8 Question 1?

9 MS. BROGDON: I think we would like
10 some comments on the four examples of
11 mitigation, the second half of Question 1.

12 CHAIR CEDARS: That's -- okay. So
13 the four -- the counseling thing, and again, I
14 think this gets to is the bar higher for
15 undergoing a procedure in a normal population
16 and how you appropriately counsel about those
17 long-term risks. This is what several of you
18 have been trying -- raising a concern about.
19 And is there a way in a trial to protect the
20 subjects of the trial from that? Dr. Gilliam?

21 DR. GILLIAM: The four suggestions
22 seem to be of different nature. The last

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1 three almost seem to ask is this woman
2 confident or able to make this decision,
3 either based on the information she has, i.e.,
4 needing a second opinion, or something about
5 her mental state, a psychological assessment
6 or having an external advocate.

7 So I think that I find the last two
8 a little -- well, the psychological
9 assessment, I find a little bit distasteful.
10 It sort of sounds as if she may not know how
11 to think through this. But the opportunity
12 for a second counseling session makes a lot of
13 sense. You could imagine if you hear it once,
14 you have a lot of questions. You do your own
15 research. You want to come back and have an
16 additional opportunity to ask questions. I
17 think that would be something that respects
18 her autonomy, but gives her the opportunity to
19 ask further questions.

20 CHAIR CEDARS: So I think the
21 concern in the sense was that that was a bit
22 paternalistic in terms of the decision

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1 process. Although, I think what the FDA was
2 trying to get at was that they had
3 non-directive advice as the genetic counselors
4 would call it. And that the physician might
5 not be as non-directive as might be required.

6 So I recognize what you are saying.

7 I think that's a valid point in terms of
8 being paternalistic toward the patient's
9 ability to make a decision. But I think their
10 goal was to make sure that they got objective
11 non- directive advice. But I think that's a
12 very valid point. Dr. Stubblefield?

13 DR. STUBBLEFIELD: Does the FDA
14 have any information about the -- how these
15 techniques have worked in practice and in any
16 area?

17 MS. BROGDON: Dr. Sarah Goldkind
18 may be able to partly address your question.

19 DR. GOLDKIND: Well, some of this
20 has grown. Some of these suggestions have
21 grown out of the informed consent literature.

22 And the recognition that studies have shown

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1 that even when informed consent has done very
2 well, subjects, potential subjects come away
3 with misconceptions.

4 One of which, one figure that's out
5 in the literature is that 50 percent of the
6 time that randomization is explained to
7 subjects, they, essentially, come away with
8 it, the understanding that the procedure that
9 is going -- the arm of the study that's going
10 to be selected for them is going to be
11 selected based on their personal
12 characteristics, not in a very objective sort
13 of protocol-driven mechanism.

14 So over the course of time, there
15 has been an attempt to try and kind of bridge
16 the gap between communication and
17 understanding. And there are many different
18 factors that influence understanding. One of
19 which is the idea of therapeutic
20 misconception, which is that they are really
21 in a study for treatment and the treatment is,
22 as said, being designed and selected for them.

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1 In this case, it is less clear that
2 they would have that misunderstanding, because
3 they are coming into the study for "treatment"
4 of a normal occurrence, physiological
5 occurrence. But the informed consent
6 literature has lots of different techniques
7 that have been suggested, some of which have
8 been studied, some of which have been
9 quantified and others are suggested for
10 helping bridge that gap.

11 And they have mentioned the
12 inclusion of the study subject advocate as
13 really an opportunity for potential subjects
14 to get a very objective take on what would be
15 involved, because there is always the concern
16 that the clinical investigator might have
17 some, you know, subtle influence over the
18 subjects enrollment, particularly if the
19 clinical investigator is also the treating
20 physician.

21 But what I can't give you right now
22 are other statistics on how some of those

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1 techniques have worked in the body of
2 literature. Some figures are out there, but
3 not -- I can't give them to you right now.

4 CHAIR CEDARS: Might I suggest to
5 the FDA something that is being utilized in
6 some of the stem cell research which is a
7 second session where they come back and there
8 is actually sort of a post test. I mean,
9 there are questions that are put together with
10 the institutional review board that they feel
11 the patient or the subject needs to understand
12 in order to go forward.

13 So it's a way to get at what the
14 subject actually understood about the consent
15 process in a post-test manner, rather than
16 bringing in a third party, which might be seen
17 as a bit more paternalistic. And so that may
18 be an option to consider as well, sort of
19 combining the more than one counseling session
20 with a post-test in terms of understanding of
21 the consent process.

22 DR. GOLDKIND: Yes, and that is

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1 also found in -- that suggestion is partially,
2 you know, explored in the informed consent
3 literature. There are lots of nuances
4 surrounding how that is accomplished, but we
5 can look at that as well.

6 CHAIR CEDARS: Dr. Zaino?

7 DR. ZAINO: Thank you. Just a
8 question having -- about the subject advocate.

9 I understand how general -- can this be
10 generalized and later when we're out of the
11 study setting and into an application in the
12 real world, can we expect that there will be
13 advocates available for the general
14 population?

15 DR. GOLDKIND: Well, that's a good
16 question and one of the -- what we have heard
17 said over and over is that, of course, the FDA
18 can't completely control the practice of
19 medicine. We can make suggestions, but we
20 can't -- we can make suggestions and, of
21 course, some of the suggestions could surround
22 that practice. Another could be restricting

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1 the age limit.

2 One of the concerns that we would
3 have is that the age limit won't truly be
4 restricted, as it is used in the general
5 population, and then you increase the regret
6 factor as has been discussed here. So how you
7 actually help minimize risk once this goes out
8 into the public medical practice is difficult.

9 And, of course, always hinges on the
10 fiduciary responsibility and trust that
11 develops between the patient and physician,
12 ultimately.

13 CHAIR CEDARS: MR. POLLARD?

14 MR. POLLARD: Yes, I would just
15 echo Sarah's comment. I think she pretty much
16 hit it spot on that we can be a little bit
17 more restrictive in the context of the
18 clinical trial if the product ever reached a
19 point where we were to approve it, we could
20 build, you know, professional and patient
21 labeling to the degree that we tried to cover
22 this as carefully as you could.

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1 We could influence a training
2 program that the company might put in place,
3 but we're very much moving into a spot where
4 the statutes clearly say there is practice of
5 medicine and there is a line there that sort
6 of goes beyond what FDA can do. Then it
7 becomes the area of ACOG Practice Bulletin and
8 other mechanisms by which your own clinical
9 community pleases itself.

10 CHAIR CEDARS: Dr. --

11 MR. POLLARD: And I would just
12 comment that --

13 CHAIR CEDARS: We need to move on.

14 MR. POLLARD: -- we've got a lot of
15 questions and this, obviously, is an important
16 point that we are going to grapple with, but
17 we asked a lot of good questions, too.

18 CHAIR CEDARS: So if we can move on
19 to study design, which gets to some of the
20 issues of inclusion and exclusion criteria
21 which addresses some of these issues. Dr.
22 Zaino?

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1 DR. ZAINO: Just in terms of
2 outcomes, I think there has been a little bit
3 of a discussion already about what the
4 appropriate outcome is and I think that is
5 probably the best question to start with. And
6 I would have to confess that I would probably
7 support having co-primary endpoints that would
8 include bleeding in some fashion and patient
9 satisfaction with method.

10 CHAIR CEDARS: Dr. Sharts-Hopko?

11 DR. SHARTS-HOPKO: Yes, I wanted to
12 build on that point and what Dr. Propert said
13 earlier. Quality of life literature is kind of
14 a big mess. People for 40 years have been
15 hashing over what is quality of life with no
16 consensus. And as was noted, I think
17 yesterday maybe, some of the tools are
18 condition-specific.

19 Nevertheless, I think you would
20 probably want to pick one. You would also be
21 able to buttress that with visual analog
22 scales that address questions like how

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1 satisfied are you that you have had this
2 procedure? And what would be your likelihood
3 of doing it again if you had it to do over
4 again? And what would be your likelihood of
5 recommending it to a close friend?

6 CHAIR CEDARS: Thank you. Others?
7 Dr. Romero?

8 DR. ROMERO: Yes, but I think the
9 specific components of satisfaction could be
10 break in - - broken down much, much in greater
11 detail that correspond with the reasons given
12 for electing the procedure to begin with. So
13 again, I reiterate that I think that would
14 require collecting that data up front, so that
15 women -- you would have self-controls, you
16 know, with regard to how they rate the
17 outcomes.

18 And I think at the same time that
19 it's really important that a control group, a
20 comparison group, not control group, be
21 seriously considered along the lines of what
22 Dr. Gilliam was suggesting.

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1 CHAIR CEDARS: So I think that to
2 do a pre and post is very important and I
3 think what about the issue in terms of the
4 fact that this is an elective procedure and so
5 should the primary outcome be an objective
6 marker or a subjective marker or usually when
7 you power a study, you have to power it for
8 your primary outcome.

9 So I'm not sure you can sort of
10 have co- outcomes, although statistics is not
11 my expertise. You would have to make sure it
12 was powered for both, but it's a little bit
13 hard to ask both of those questions. And I
14 think that's relevant for an elective type
15 procedure. Dr. Peterson?

16 DR. PETERSON: I think that's real
17 important. If -- there will have to be
18 primary endpoints that you power. There are a
19 series of outcome measures that seem to have
20 already been determined to be paramount here
21 and it goes back to the question about
22 indication and say well, the indication is

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1 granted if under these circumstances, it's
2 safe and it's effective.

3 Well, the problem here is safe and
4 compared to what? Effective and compared to
5 what? And then we have to say well, what are
6 the measures? What is the truth that we are
7 trying to demonstrate? Safe with regard to
8 what, compared to what? Effective with regard
9 to what, compared to what? And to design the
10 study, we have to initially make that
11 determination.

12 What is it that we are considering
13 safe? I mean, what are the safety issues?
14 And we have to identify those. And we have to
15 decide which are most important and power the
16 study accordingly. Effectiveness, what are we
17 really talking about? Is it the bleeding is
18 the only issue? Is it quality of life? Is it
19 the molimina that Paul was talking about?

20 You know, we have to decide what
21 the effectiveness issues for this indication
22 that we're trying to demonstrate and then

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1 design the trial accordingly. And then decide
2 if we can just say okay, all we want is point
3 estimates with a reasonable range of certainty
4 about those outcomes or we're going to say
5 compared to what?

6 And that's the problem that's still
7 getting to me is that right now there isn't a
8 practice out there for this indication. And
9 so we are creating a solution to -- a new one
10 and don't have an alternate practice compared
11 to what? So I don't see how we can design the
12 trial until we figure out what it is we are
13 trying to demonstrate.

14 CHAIR CEDARS: Ms. Brogdon, did you
15 want to respond to that?

16 MS. BROGDON: No.

17 CHAIR CEDARS: Dr. Davis?

18 DR. DAVIS: If you look at the --

19 CHAIR CEDARS: Can you turn your
20 mike on, please?

21 DR. DAVIS: If you look at the
22 study that has been alluded to several times,

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1 the Stop DUB, the randomized control trial,
2 they had in much more detail, as you
3 mentioned, their primary reason was most of
4 the subjects was bleeding. Now, again, we
5 don't have bleeding in this one. But the
6 primary endpoint was did that improve?

7 So if you took what the primary
8 reason was for the people in this study, which
9 would likely be given the data that we do have
10 limited, interference with sexual lives,
11 sports or work and then did that improve with
12 much more evaluation of those, those are
13 endpoints that are doable. Again, I'm not
14 saying I like the idea, but it is something
15 that you could quantitate.

16 CHAIR CEDARS: Dr. Gilliam?

17 DR. GILLIAM: If you look at that
18 Stop DUB Study as our speaker pointed out, a
19 lot of those women had to undergo
20 re-operations, which in that case was a
21 hysterectomy, which indicates that this is a
22 procedure that has quite a bit of risk and

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1 also a chance of failure. Therefore, the bar
2 has to be set very, very high for an elective
3 procedure that could fail, have unknown
4 consequences.

5 Quality of life, you will be able
6 to find some difference in numbers and then
7 you will be able to actually achieve an
8 outcome and achieve your indication if you use
9 something, a secondary outcome. And I would
10 say that's a secondary outcome like quality of
11 life. I would say you choose the hardest
12 clinical outcome and it has to be -- and I
13 feel this is almost like a methodic experiment
14 in some ways, because I think we have to -- we
15 have never clearly grappled with the ethical
16 question of is this study like this justified,
17 given the potential risk that we know from its
18 other uses?

19 But given that we are just going to
20 set that aside, I think, if we are really
21 seriously thinking about doing a clinical
22 trial of something that is an elective

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1 procedure, the bar has to be very, very high
2 in regard to safety and the only way that you
3 are going to get those numbers is to have a
4 very hard clinical outcome that has to be
5 achieved.

6 As soon as you say amenorrhea is
7 okay and a little bit of spotting and the
8 spotting can occur on this many days, you will
9 -- if the target is big enough, you're going
10 to be able to reach it and you're not going to
11 need as big an effect size and so you will
12 need a smaller population. And I think what
13 we should do is set the highest criterion, so
14 that we have a large study and we can really
15 understand what this is about before we
16 unleash it on the population.

17 CHAIR CEDARS: Dr. Stubblefield?

18 DR. STUBBLEFIELD: Well, several
19 things that continue in that vein. Even
20 though the FDA can't officially compare to
21 long-term use of the pill or the IUD, perhaps,
22 in the real world that's what women are

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1 deciding to do already is use these
2 alternative methods if they have menstrual
3 problems.

4 Both of those alternative methods
5 go way beyond preventing or reducing bleeding.

6 They also reduce the menstrual molimina,
7 especially the long interval with the pill.
8 Women whose headaches haven't responded to
9 anything else, women whose PMS hasn't
10 responded to anything else have gotten relief
11 from long-term use of the pill. I mean, long
12 interval without menstruation.

13 So pretty clearly, if we do get
14 into a study, we need that kind of comparative
15 information. We need to look for those items,
16 not just bleeding. We need to look at
17 menstrual molimina, other menstrual cycle-
18 related symptoms and migraine headaches,
19 etcetera, which continues, I think, what Paul
20 raised about women may think it's the bleeding
21 they don't want to have, but it may likely be
22 everything else.

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1 And so we need to capture the
2 everything else, so that we can see, in fact,
3 are the women not bleeding, but still
4 miserable? Is your sex life still terrible?
5 You know, all of those things are going to
6 need to be looked at. The global patient
7 care. And if we just focus on the bleeding,
8 we'll be doing the patients a big disservice.

9 And also, we need to do this as we
10 heard from Dr. McCausland for a long time, the
11 study needs to be four or five years, so at
12 least we are able to get the beginning of what
13 we might see.

14 DR. GILLIAM: Can I just clarify?

15 CHAIR CEDARS: One more comment.

16 DR. GILLIAM: Okay. I just wanted
17 to be clear. I am talking about what you
18 power it on. I think once you set up a study
19 with this many women, you measure everything
20 under the sun. But I want you to power it
21 very, very conservatively, rather than on a
22 less conservative outcome.

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1 CHAIR CEDARS: Dr. Propert?

2 DR. PROPERT: I guess, I work in a
3 lot of multi-dimensional illnesses where
4 people have 10 problems and they can't
5 necessarily say which is worse. So I agree
6 you should power it most conservatively, but I
7 think you need to look at data from other
8 studies to find out which of potentially a lot
9 of endpoints might be the most conservative
10 one. And I'm not convinced it is bleeding
11 here.

12 CHAIR CEDARS: And I think that
13 this -- we also need to look at this as two
14 sided, because these people could get worse,
15 rather than bleeding for three days once a
16 month. Now, they are bleeding continuously.
17 Bleeding may be more of a complaint. They may
18 get an increase in dysmenorrhea based on Dr.
19 -- what Dr. McCausland had to say.

20 So their symptoms may actually get
21 worse and not better. So I think
22 statistically that's going to be important as

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1 well. So if we can close out the outcome
2 discussion and then we can go, because people
3 felt like we needed an outcome before we could
4 go to inclusion and exclusion criteria. So
5 the primary outcome, because again, I think
6 you have to have a primary outcome in terms of
7 powering it, is it bleeding? Is it quality of
8 life issues? Is it before and after? Do we
9 have a sense of what that is, so we can help
10 the FDA with this? Dr. Sharts-Hopko?

11 DR. SHARTS-HOPKO: I don't know if
12 it is particularly helpful, but there are
13 menstrual quality of life tools that
14 incorporate various facets of the menstrual
15 experience.

16 CHAIR CEDARS: Do you have enough
17 issues on that, Ms. Brogdon?

18 MS. BROGDON: Yes, thank you.

19 CHAIR CEDARS: Okay. So if we
20 assume that there is some combination of
21 bleeding and let me ask one other question.
22 Do we want to set the bar at -- for bleeding,

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1 because clearly there are issues about quality
2 of life. Do we want to set the bar for
3 bleeding at amenorrhea or amenorrhea plus
4 spotting? Where is the bar? Does it need to
5 be higher for this? Dr. Romero?

6 DR. ROMERO: Amenorrhea.

7 CHAIR CEDARS: Dr. Snyder?

8 DR. SNYDER: It doesn't make sense
9 to me from the standpoint that we have already
10 got, you know, early data. I mean, we have
11 got a wealth of data on pivotal trials, other
12 trials and everything. I mean, we've got a
13 chart in here that tells you what the
14 amenorrhea rate is.

15 So, you know, I'm in the camp where
16 if you've got something that is being done on
17 an elective basis, there is only one endpoint.
18 The happy or not happy. But then, since I'm
19 talking now, I'm struggling, you know, Dr.
20 Gilliam mentioned that we have set aside the
21 basic issue, which is is this even doable, and
22 we're trying to figure out how to do it, but

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1 I'm not -- you know, I don't think we have
2 answered the original question, which is is
3 this, you know, something that we would
4 recommend to be done at all.

5 CHAIR CEDARS: Dr. Romero?

6 DR. ROMERO: I don't think we were
7 asked that question. And I'm -- you know, if
8 we were asked that question, I don't know if
9 we would be having this conversation now.

10 CHAIR CEDARS: Right. I think that
11 question wasn't put to us. The question was
12 just if this were done, what is the best way
13 to do it? Because I think that it's pretty
14 clear the consensus around the table is there
15 is a lot of dis-ease with this as a concept.
16 So assuming this were going to be done, what
17 would be the best way to do it? Dr. Sharp?

18 DR. SHARP: I would say in terms of
19 the endpoint of bleeding, I would think
20 amenorrhea would need to be the endpoint. If
21 your PBLAC score is 5, you know, we don't know
22 what it is going to be, because it's normal

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1 already. So I would have to think that
2 amenorrhea would be the logical endpoint for
3 bleeding.

4 CHAIR CEDARS: And just in response
5 to Dr. Snyder, the problem with utilizing that
6 data in terms of establishment of amenorrhea
7 is these were patients with menorrhagia and
8 establishing amenorrhea in that patient cohort
9 may be different than establishing amenorrhea
10 in a cohort of normally menstruating women.

11 So amenorrhea as the bleeding
12 endpoint, I think, there is a general
13 consensus and then very clearly and some
14 debate still about which takes prominence in
15 terms of quality of life issues and whether
16 the patient is happy, whether she would do it
17 again, whether she would recommend it to a
18 friend, etcetera, needs to be if not the
19 primary very closely.

20 So given those two endpoints in
21 some hierarchial state, what would be the
22 inclusion/exclusion criteria that patients --

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1 or that the Panel would suggest? Dr. Romero?
2 No, no. Dr. Sharts-Hopko?

3 DR. SHARTS-HOPKO: It was suggested
4 to us that maybe we would want to include
5 women who have already been sterilized who are
6 still fertile. So I could go with that.

7 CHAIR CEDARS: So an inclusion
8 criteria that they have undergone a
9 sterilization procedure. There was a concern
10 by Dr. Sharp that, one, we may be setting
11 people up for more complications in terms of
12 Dr. McCausland's discussion and, two, we would
13 then not get information about the people that
14 weren't sterilized and what happened with
15 them. Is there any other discussion on this
16 point?

17 I think one of the key issues and I
18 hate to keep coming back to this, but I know
19 it's an issue for all of us is that if you are
20 requiring contraception, these people still
21 need some form of contraception and you're not
22 going to require permanent sterilization ahead

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1 of time, then not only does it beg the
2 question again of a comparator group, but you
3 may -- they may also use something as a
4 contraceptive that affects their bleeding. And
5 so the outcome in terms of bleeding and
6 symptoms may be impacted more by what they use
7 as their contraceptive than the actual first
8 procedure. So I think that's an issue as
9 well.

10 There was a suggestion about age.
11 Would there be any consensus should there be a
12 lower age limit for this study for an
13 inclusion criteria, given the issue of regret
14 and remarriage and thinking you are finished
15 with childbearing and then not being? Dr.
16 Hillard?

17 DR. HILLARD: If you accept the
18 criterion of previous sterilization, then I
19 would say that would obviate the need for an
20 age criteria.

21 CHAIR CEDARS: How comfortable are
22 people with the concept of presterilization?

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1 Because that was a specific question that the
2 FDA had. Is that a plus or a negative for this
3 study or neutral? Dr. Sharp?

4 DR. SHARP: Well, we don't know the
5 answer to that, that's why it might be good to
6 know. I was just going to say on age, we kind
7 of have two issues with that as well, because
8 certainly if you said well, we'll put the age
9 at 40, certainly you have less of an issue
10 with pregnancy and maybe some of the regret
11 issues. But then again, you don't get the
12 information that how is this affecting those
13 who are younger? So it is kind of a double
14 edge sword.

15 CHAIR CEDARS: So then since age is
16 relevant to the previous sterilization, is
17 there a consensus in terms of requiring or not
18 requiring prior permanent sterilization? Dr.
19 Romero?

20 DR. ROMERO: If I try to go in my
21 mind through a logical sort of line of
22 thinking around the concerns associated with

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1 this kind of a procedure, it seems that I end
2 up at a place thinking that women who have
3 been sterilized should be the specific target
4 group here. But then that means -- and I
5 agree, then I think it possibly eliminates
6 some of the concerns.

7 But then that presents a quandary
8 around whether women who weren't thinking of
9 seeking -- who were not previously sterilized
10 weren't thinking of it, were just thinking of
11 endometrial ablation for, you know, these
12 reasons, then are somewhat encouraged to
13 consider sterilization.

14 And then I'm sort of looped around
15 again thinking well, maybe if anything that's
16 a good thing because this procedure while not
17 guaranteeing sterilization is highly likely to
18 be associated with that. So I think that my
19 thinking around this is very convoluted. And
20 I'm inclined to say if putting aside the
21 question as to whether this is appropriate,
22 I'm inclined to say that maybe this criterion,

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1 inclusion criterion of sterilization makes the
2 most sense. But that's with a huge caveat
3 that I'm still unresolved around proceeding
4 down this path.

5 CHAIR CEDARS: Dr. Snyder?

6 DR. SNYDER: Yes, I'm more than
7 convoluted on this whole thing. But if the --
8 if one of our big long-term goals is safety, I
9 think this sterilization is, you know, an
10 absolute inclusion criterion that we have
11 already heard on, you know, other issues that
12 no matter how much patients understand that,
13 there are going -- if they are still at
14 significant risk of pregnancy, we're going to
15 see, you know, problems.

16 And so if we're doing this and
17 safety is an endpoint, I would think we would
18 want to start with permanent sterilization.

19 CHAIR CEDARS: Dr. Peterson?

20 DR. PETERSON: Yes, I mean, I think
21 the convoluted part is something that is not a
22 lack of clear thinking on our part. I think

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1 that when you think about what we're
2 struggling with, the struggle is related to
3 this being, I think, one of the most -- more
4 ethically and scientifically challenging
5 exercises I have been a part of in several
6 decades.

7 This is not a simple
8 straightforward matter ethically or
9 scientifically. And I think that's the
10 difficulty. And I'm not sure how we can be
11 most helpful. This is a forest and trees
12 thing and a lot of what we're talking about
13 are specific trees and the forest question
14 hasn't been addressed.

15 And, you know, one, in terms of
16 exposures and outcomes, we've still got the
17 issue about outcomes and we're coming closer
18 to getting the outcome on effectiveness and
19 trying to decide what is effective.

20 We still haven't gotten to the
21 issue about safe and what is safe, because
22 we've got short and long-term measures that we

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1 have to identify. And then we still haven't
2 identified the safe and effective compared to
3 what and whether or not there is another group
4 of people that needs to be followed.

5 And now, we're talking about who is
6 to include and exclude and part of the issue
7 is about including and excluding scientific in
8 terms of comparability and scientific in terms
9 of generalizability and what indication would
10 be ultimately approved based on these data.
11 And part of it is ethical. Who is it ethical
12 to experiment on in this sea of uncertainty?

13 So, I mean, I think there are quite
14 a few important issues that we haven't been
15 able to address yet.

16 CHAIR CEDARS: Mr. Pollard?

17 MR. POLLARD: I think your point is
18 very well taken. And you know, we still have
19 several questions to go and I know we don't
20 have much more time allocated. One of the
21 things that we're taking away from this
22 discussion is a lot more exploration needs to

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1 be done into a number of areas, where these
2 questions are going.

3 And if there isn't going to be some
4 nice pat answer from the Panel, either
5 individually or collectively, so maybe for the
6 rest of the course making your way through,
7 rather than try to come up with a, you know,
8 nice singular take away answer, suggestions
9 for us to -- because we definitely already
10 heard three or four different areas where
11 we're, obviously, going to have to go back and
12 explore different possibilities and really try
13 to figure out how to weigh them together,
14 because I agree, it is a complex question.

15 So I would just say maybe for the
16 remainder of the discussion, just use this as
17 an opportunity to give us some ideas about
18 where to continue exploring and we may wind
19 up, you know, tapping one or more of you to
20 help us sort through some of those as we go
21 along.

22 CHAIR CEDARS: Thank you. That's

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1 helpful. Dr. Snyder?

2 DR. SNYDER: Then let me use that
3 as a segue into one of my other concerns. I
4 was really struggling, you know, with last
5 night with this, because again one of our
6 endpoints has got to be is it safe? Then I
7 think we have a duty to make sure that we are
8 including in the trial, you know, patients
9 that are least likely to have a problem.

10 And so, you know, one of -- and I
11 would want to hear what other people have to
12 say. I think the issue of whether they are
13 ovulatory or not has got to be discussed.
14 That wasn't as big an issue, I think when the
15 topic was treatment of menorrhagia. I mean,
16 there is a medical treatment of menorrhagia.
17 If that gets failed, then the norm was
18 hysterectomy.

19 Well, they are talking about a
20 procedure that might potentially avert
21 hysterectomies. Okay. But in most -- we heard
22 that there is different definitions of

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1 menorrhagia, but the true medical definition
2 is cyclical, you know, heavy menses, which
3 excludes most women that are, you know, not
4 ovulatory or oligo- ovulatory. And those are
5 the patients that I've got a whole lot of
6 concern about that would not necessarily be,
7 you know, eliminated as an inclusion criteria
8 if we didn't specifically discuss it.

9 Because if they are in, you know,
10 chronic estrous, they are at increased risk
11 for endometrial carcinoma and Dr. Peterson
12 mentioned they are short and long-term. I
13 think we really need to consider there being
14 short-term problems with the procedure, you
15 know, burns and so forth. There is the
16 midterm problems and that's the PATSS and
17 everything else.

18 And then the long-term risk though
19 is, you know, what is going to happen, you
20 know, in the -- you know, with the risk of
21 endometrial carcinoma and that goes on, you
22 know, for a long time. So I'm just, you know,

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1 very concerned that if we don't address that
2 issue --

3 CHAIR CEDARS: Yes, I agree that
4 wasn't specifically mentioned. I guess my
5 assumption it had to do with inclusion and
6 exclusion criteria that these were ovulatory,
7 that these were women with normal regular
8 menstrual cycles. Yes?

9 DR. SNYDER: Well, and then see
10 then the reason I started getting so confused
11 is because now, let's just look at the natural
12 -- you know, what happens in the later
13 reproductive years. Women who are ovulatory,
14 you know, the natural sequence is to become
15 oligo-ovulatory, anovulatory and then have
16 cessation. You see, what I mean?

17 CHAIR CEDARS: Correct, yes. Dr.
18 Hillard?

19 DR. HILLARD: And of course, we all
20 understand it, but to state the obvious
21 though, the other groups, the PCOS women again
22 they may or may not have regular menses, but

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1 the other group is women who are obese. And
2 so we are concerned about that. So do we have
3 a weight cutoff in this group?

4 CHAIR CEDARS: The FDA has given us
5 a little bit more leeway, can I ask a
6 question, because I think this would be
7 something that would be important for study
8 design and is something that is important for
9 the Panel. If it's possible for the FDA, if
10 we can go back and talk about a control group,
11 and whether or not there should be a treatment
12 arm? Can we -- are we at liberty to discuss
13 that or no, since there is no other treatment
14 that's approved for this indication?

15 MR. POLLARD: I mean, you have a
16 lot of discretion as Panel Chairperson, okay.

17 And that being said, I would say it's kind of
18 up to you to decide how you want to use your
19 last few minutes here. You have obviously --
20 I mean, I was just talking to Veronica and you
21 kind of covered the study outcome questions to
22 5 and 6 and 7, although, obviously, there is a

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1 little bit more drilling into that, if we get
2 the take away from your message of what we
3 need to do, maybe some more interactions with
4 sponsors who are interested and maybe some
5 more work on our own part to do that.

6 I'm certainly not going to say no,
7 you can't go back and talk about control, so
8 it's all just a matter of, you know, what you
9 want to do with your last few minutes.

10 CHAIR CEDARS: I mean, I get a
11 sense that that's a really critical issue for
12 a lot of the Panel Members and that they would
13 be happier with a study that's looking at an
14 elective procedure given the availability of
15 both intrauterine systems and long interval
16 OCPs and the requirement for some form of
17 contraception, because of the risk of
18 pregnancy after an ablation that it's kind of
19 the elephant in the room.

20 And so I guess I feel like that is
21 an important issue. Am I misreading? It
22 sounds like there is consensus from the Panel.

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1 So I think for us, that is an important issue
2 and I think needs to be discussed. Ms.
3 George?

4 MS. GEORGE: We were talking
5 earlier about other elective type things. I
6 know it's not an OB GYN area, but has the FDA
7 looked at all at like the laser surgery
8 elective, since that's elective and there is
9 contacts and there is glasses? I know there
10 was a huge study done on that, because my
11 husband was actually one of the participants
12 as a patient. So I'm just curious if that has
13 been compared?

14 MS. BROGDON: That's what I meant
15 when I referred to refractive procedures
16 earlier.

17 MS. GEORGE: Oh, okay.

18 MS. BROGDON: That kind of
19 underlaid the discussions, but it was never
20 discussed specifically.

21 CHAIR CEDARS: Yes, I think the
22 difference with that is that you are still

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1 going to require contraception with this
2 technique. So it's not like you're going to
3 do this and you are going to get -- you are
4 still going to have to use contraception,
5 because one of the complications is pregnancy.

6 And so it, in my mind, sort of begs the
7 question, even though there is not another
8 indication if you are going to require and
9 that gets a bit toward the inclusion/
10 exclusion criteria, because if the inclusion
11 criteria were either you required permanent
12 sterilization or you require the person to be
13 using some alternative contraception, because
14 they need to and that should be part of the
15 inclusion criteria, then I think it begs the
16 question of another control group.

17 MR. POLLARD: And the thing I would
18 add, we have had some very preliminary
19 discussions with our colleagues over the
20 Center for Drug Evaluation and Research, CDER,
21 and had some of these same kind of
22 discussions, although just at a cursory level.

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1 You know, as you know, there is at least one
2 or two oral contraceptives that although their
3 indication is contraception, they are
4 permitted a product claim associated with
5 menses suppression.

6 You know, so that is arguably a
7 possible control arm. It would be interesting
8 to hear what the panel thinks about that,
9 because if you're talking about control,
10 you're talking about a randomized control,
11 obviously one is reversible, one is not
12 reversible. Not -- still not that simple a
13 situation.

14 CHAIR CEDARS: Dr. Snyder?

15 DR. SNYDER: Well, and that's what
16 I really struggled with. I too would like to
17 see the control group be, you know, continuous
18 or extended duration oral contraceptives, a
19 second control group being women with the
20 Levonorgestrel IUD and, you know, the third
21 group being this.

22 But the problem, you know, that

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1 comes in is that the world contraceptives,
2 besides providing contraception provide, you
3 know, control of bleeding, they control --
4 have also protection against endometrial
5 carcinoma. The IUD, protection against
6 pregnancy, protection against endometrial
7 carcinoma and an effect on bleeding.
8 Endometrial ablation, just bleeding.

9 CHAIR CEDARS: But I think that if
10 you are looking at an elective endpoint, then
11 those are valid options for the patient who
12 wants cessation of menses and that's the
13 comparison the patient is going to have in
14 front of them. And so to make the study be
15 sort of real world, I think you need to
16 include those things that are real world for
17 the patient. Dr. Stubblefield?

18 DR. STUBBLEFIELD: I think we
19 should have those control groups, but to state
20 the obvious that does introduce the complexity
21 of your inclusions and exclusions. You have
22 to have people for whom oral contraceptives

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1 are not excluded or are not at high risk. We
2 would probably be wanting to include heavy
3 women, they are more apt to have bleeding
4 troubles that aren't bad enough for
5 menorrhagia, but are bothering them and yet,
6 they are at increased risk for thrombosis on
7 oral contraceptives.

8 CHAIR CEDARS: A valid point.
9 Other discussion? Are there any key questions
10 that you want to make sure that we get
11 covered, either Nancy or Colin?

12 MS. BROGDON: No, we don't think
13 so.

14 CHAIR CEDARS: Okay.

15 MS. BROGDON: Colin will speak to
16 this.

17 MR. POLLARD: One question we did
18 want and it's sort of flash forwarding a few
19 questions to that last question. We would
20 like to get a little discussion of this issue
21 relating to masking the diagnosis or delaying
22 the diagnosis of uterine cancer with respect

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1 to the patient population. How we would -- is
2 this something we need to be concerned about?
3 If so, are there any, you know, provisions in
4 a trial that we really should be thinking
5 about?

6 CHAIR CEDARS: So issues about the
7 risk of masking uterine cancer. I think Dr.
8 Snyder has already brought up the issue of
9 patients who are anovulatory and I agree those
10 patients should be excluded. The issue of
11 patients becoming anovulatory as they get
12 older is true for even the patients who had an
13 ablation and may be more so of a risk for the
14 patients who had an ablation under the current
15 protocols.

16 So would there be any unique issues
17 about this elective population in terms of the
18 risk? Dr. Zaino?

19 DR. ZAINO: I think the Lynch
20 Syndrome would have to be considered. So I'm
21 not sure of what screening you would want to
22 include, but they probably should not include

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1 that population.

2 CHAIR CEDARS: I'm sorry, the?

3 DR. ZAINO: Lynch. The hereditary
4 nonpolyposis colon cancer patients who have
5 got a 40 to 60 percent lifetime risk of
6 developing endometrial cancer.

7 CHAIR CEDARS: Any other specific
8 exclusions? What about a weight limit with
9 respect to endometrial cancer? That was
10 raised as an issue. Well, of course, it was
11 also raised that that might be the patient who
12 would most be looking for some non-hormonal
13 alternative for menstrual cessation, because
14 of the risks with hormonal care. Dr. Davis?

15 DR. DAVIS: That becomes very
16 difficult and if you look at the Stop DUB
17 Study, very high proportion of their women
18 were obese and a very high proportion were
19 morbidly obese, so boy, you are excluding a
20 big part of your population there.

21 CHAIR CEDARS: Well, a big part of
22 our nation's population. Dr. Zaino?

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1 DR. ZAINO: I guess one other thing
2 I would suggest is that the design probably
3 should include a prestudy endometrial sampling
4 to exclude any pathology.

5 CHAIR CEDARS: Okay. Presampling.
6 Any other issues with respect to the uterine
7 cancer? And then let me kind of go backwards
8 up since we have got just a few minutes. And
9 one of the questions was about questionnaires
10 and whether or not they would need to be
11 validated in this population, since we
12 struggled a lot with what the sort of quality
13 of life issues would be.

14 Most of them have not been
15 validated in the normal cycling woman and so
16 would we need to have a validated
17 questionnaire to utilize that? Dr. Probert?

18 DR. PROPERT: The problem with it,
19 there are two types of validation. There is
20 validating that it is doing the right thing
21 and then there is validating that it is giving
22 you appropriate measures that change in a

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1 clinical trial. And the only way to do the
2 second one is to put it in a trial.

3 So I would like to see them be
4 validated in terms of, you know, those alpha
5 things and all the things that you are
6 supposed to do. But I think the only way you
7 can validate whether it is measuring what you
8 want it to measure is to put it in a trial you
9 are going to do it in.

10 CHAIR CEDARS: And then one other
11 thing that we skipped and we mentioned it
12 early on, but not specifically relevant to
13 Question No. 8 was given that this is an
14 elective procedure, would the rate of adverse
15 events or would our threshold for adverse
16 events be lower? And I think there is a
17 general consensus that our tolerance for
18 adverse events would be much lower, given that
19 this is an elective procedure.

20 And then otherwise, I think we
21 actually in a bit of a round about way covered
22 most of your questions. Are there other

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1 specific issues, Nancy, that --

2 MS. BROGDON: No, thank you very
3 much.

4 CHAIR CEDARS: If not, then I would
5 adjourn this session of the Obstetrics and
6 Gynecology Devices Panel. Thank you all for
7 your time and safe travels home.

8 MS. BROGDON: And thank you to all
9 the Panel for all of the time and energy you
10 spent in preparing and for giving us your
11 expert advice. Thank you.

12 (Whereupon, the meeting was
13 concluded at 1:18 p.m.)

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