An Ethical Consent Form: Phase 1 dose escalation study of anti-CD22 chimeric receptor T cells

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Consent forms can be overwhelming for patients to read and exhausting for medical investigators to get approved, but they are essential for protecting both parties during research on human subjects. Before enrolling, human subjects must be aware of their options and rights, as well as the qualifications to participate, study procedures, side effects, patient benefits and other aspects of the study. These facts allow patients to make an informed decision about whether or not a study is a good choice for them. Prior to FDA approval, drugs must be proven safe and effective for humans in clinical trials, so there are many studies for new cancer drugs and protocols. Investigator Terry J. Fry of the National Cancer Institute did a thorough job addressing safety, side effects, benefit to the patient and other important issues in the consent form for his Phase 1 Dose Escalation Study of Anti-CD22 Chimeric Receptor T Cells in Pediatric and Young Adults with Recurrent of Refractory CD22-expressing B Cell Malignancies.

With this study, Dr. Fry and his team are testing the safety, and to some extent the efficacy, of killing CD22 positive leukemia or lymphoma cells with modified T cells. A similar method has already been used to treat patients with CD19 positive blood cancers but this is the first study targeting CD22 with modified T cells. (T.J. Fry, personal communication, October 19, 2015)

The National Institute of Mental Health released a video in 2013 about the necessary elements of a successful informed consent. The video followed the Common Rule guidelines, more formally known as Protection of Human Services, Title 45, part 46 of the Code of Federal Regulations. The video mentioned certain topics and sections that must be present in an informed consent document, including the introduction, purpose, qualifications to participate, study procedures, alternative treatment options, risks and benefits, conflicts of interest, and privacy. All of these sections were present in the consent form for the anti-CD22 chimeric receptor T cell

study. The introduction of the consent form shares the purpose of the study and makes it clear to patients that participation in the study is voluntary and they have the right to withdraw at any time. The consent form mentions in multiple places that the purpose of the study is not primarily to benefit the patient. The first page of the introduction gets right to the point: "You may receive no benefit from taking part. The research may give us knowledge that may help people in the future" (Fry, 2015, 1). The next page reinforces this: "The primary purpose is to test for safety, to see how the intervention affects the body, to test for harms and discomforts, and to see how the side effects change at different doses. In this study we will also test whether or not the intervention has any beneficial effects" (Fry, 2015, 2). The study may be beneficial to patients, but it is clear that the main purpose is research. It is critical that this detail is clearly communicated with patients during the consent discussion as well, because many patients do not understand that the trial is not necessarily for their benefit. Patients in first-phase oncology trials may be stressed and in pain which can make it especially difficult to process all the information in the consent form. "It has been demonstrated by empirical studies of informed consent that only 33% of the research participants clearly understood that the main purpose of such a trial was to help future patients rather than hope for his or her own benefit" (Gefenas, 2007, 283). Dr. Fry's consent form addressed this issue throughout, which may help increase the number of patients who understand the true goals of the study.

The qualifications to participate, duration, and study procedures are presented together. The most important qualification is that patients have leukemia or lymphoma expressing the CD22 protein. Once this has been determined, there are a number of other required tests to determine eligibility. The study procedures are presented in a simple bulleted list, which makes them easy to understand. Among other things, spinal fluid samples and a bone marrow aspiration

and biopsy are required in order to determine eligibility. After patients are deemed eligible, there is a list of additional tests that are required before starting the chemotherapy. These include a physical exam, eye exam, blood and urine tests and a neurologic evaluation. (Fry, 2015, 3-4) Following the bulleted list of study procedures, the cell collection, chemotherapy, cell infusion and follow up process are clarified in more detail. The leukapheresis procedure is outlined in simple language and the chemotherapy schedule and lengths of infusions are provided. The amount of blood required for research blood tests is also specified for certain days relative to the cell infusion. The follow up procedures are rather general because they depend on the patient's response and whether or not they go on to other therapies.

After the bulleted list and detailed procedures, these details are presented again in a chart format which organizes the schedule by day. This chart appears to contain all of the same information that was just presented, except there is one important addition on the second page of the chart. On day -4, "if it has been longer than 14 days since your disease evaluation, it will be repeated" (Fry, 2015, 8). In such a long document, it is tempting to flip quickly through this chart after looking at the first page and seeing it is a summary of information that was already presented. However, if patients do this, they will not know about these extra tests even though all of the other tests are mentioned repeatedly. Cell processing can be delayed up to 30 days after cell collection, and the modification process can take a week or two which means some patients will need the bone marrow aspiration and biopsy repeated, even after they have been deemed eligible for the study. (Fry, 2015, 4) This information should be discussed in the consent signing meeting, and it would be beneficial for patients if it was presented in the bulleted list and detailed procedures as well.

Birth control is addressed at the end of the study procedures section because if a woman becomes pregnant, she will be taken off the study immediately. It is important that participants use methods to avoid getting pregnant or fathering children during the study. (Fry, 2015, 9) The consent form also clarifies that no chemotherapy is to be given between the cell harvesting and the start of the fludarabine for the prep regimen. (Fry, 2015, 4) Other medications, vitamins and herbal supplements are not addressed, but the doctors ask about these during the consent meeting.

Alternative treatment options are provided in the consent form, and unlike many phase one oncology studies, some patients do have a few options in addition to palliative care, including standard chemotherapy and bone marrow transplant. The form encourages patients to talk to their doctor about the other options. (Fry, 2015, 9) It is especially important that patients know their options to make an informed decision before consenting to a study that may not be for their benefit. (Protection of Human Subjects, 2009).

The risks and discomforts section of the consent form maintains a very serious tone, reminding patients that "this study includes a serious form of experimental intervention with several possible risks" (Fry, 2015, 9). Just like patients need to understand that a phase one trial is for future benefit, they also need to understand that not all of the risks are known, and this consent form makes that clear: "doctors don't know all the side effects that may happen" (Fry, 2015, 9). The risks of the CAR cells and each chemotherapy drug are presented in charts showing rare, less common, and uncommon side effects. These likelihoods are clearly defined, with rare side effects occurring in three or fewer patients out of 100, less common occurring in four to twenty patients, and common occurring in more than twenty. A few of the side effects, such as cytokine release syndrome and autoimmune reaction, which patients may be unfamiliar

with, are italicized and then explained in more detail on the next page. Cytokine release syndrome can cause serious side effects, and if it gets too bad it can be treated with a drug called Tocilizumab. The consent clarifies that this medicine has been FDA approved for rheumatoid arthritis but is still experimental for cytokine storms. (Fry, 2015, 11) In addition to the risks from the study drugs, the support medications are presented in the same convenient chart format. Each chart is accompanied by a brief description of what the drug is for, such as "to prevent bleeding in the bladder from cyclophosphamide" (Fry, 2015, 13). Risks for routine procedures such as blood draws, bone marrow aspirations and apheresis are also listed.

Since this is a phase one study, the first time this specific therapy has been used on humans, the risks cannot all be known. The consent form provides what it can about the known risks, and discusses other studies that may suggest additional possible risks for this study. For example, the consent form mentions that two patients have died from receiving CAR cells, one patient at NIH and one patient at another hospital, during a similar trial targeting CD19 instead of CD22. The consent form also mentions potential issues with the immune system, nerves, or even a secondary blood cancer. It explains that in a gene therapy study in France and England, some of the patients later developed leukemia caused by the gene therapy, though improvements have been made since then to reduce the risk. (Fry, 2015, 15-16)

The potential benefits of participation section once again makes it clear that this treatment is for research and to help others in the future. "The aim of this study is to see if this experimental intervention is safe and if it will decrease the amount of your cancer. This experimental intervention has not been given previously to patients, so we do not know if it will benefit you." (Fry, 2015, 16) The goal is to see if the treatment is safe, and it would be misleading to suggest a likely benefit to the patient.

The consent states that “new information that becomes available during the course of this study that may impact your willingness to participate will be shared with you” (Fry, 2015, 12). As this is such a new protocol with less than ten patients treated, the doctors have followed through with this and done a thorough job of updating new patients on the status of previous patients as soon as possible.

The privacy section of this consent form is very short. Dr. Fry is named as the sponsor and “records may be reviewed by NIH organizations and by organizations outside the National Institutes of Health, such as representatives of the US Food and Drug Administration. Every effort will be made to protect your privacy in any recording or reporting of this information” (Fry, 2015, 17). This sounds like there is not much guarantee of privacy internally among research staff, though names and identifying information will not be shared externally in scientific journals or meetings. The Federal Privacy Act protects medical records but allows some information to be viewed by the FDA, Congress, law enforcement or hospital accreditation organizations. (Fry, 2015, 19)

Conflict of interest is addressed near the end of the consent form. This section informs patients about anyone who may benefit from the study. It notes that information from this study “may become valuable for commercial research and development purposes (including patentable inventions), which may be of significant benefit to society, the sponsor of this study, individual researchers or other third parties” (Fry, 2015, 18) but the patients will not receive any financial benefit. The form also discloses that the National Institutes of Health and one of the investigators have a patent pending for one of the components of the study. (Fry, 2015, 18)

The informational part of the consent form ends with other important information, which includes the last few elements of a successful informed consent form that the video and Common

Rule discuss. This page discusses confidentiality, policy regarding research-related injuries, payments, and who to contact with problems or questions or if a participant changes their mind about enrolling in the study. Finally, the last page has a space for the signatures of the patient, parent or guardian for minors, investigator and a witness.

In addition to the important elements of a consent form, the National Institute of Mental Health video included guidelines for the consent meeting between the patient and doctor. The consent form is given to patients in advance of the signing meeting and patients are encouraged to read it closely and write comments in the margins. Patients are asked if they have any questions before they begin the consenting process, which is conversational. The patient is allowed to have parents in the room during the conversation to make it more comfortable.

Not all patients have a scientific background or even significant education, so it is important that consent forms use language appropriate for an eighth-grade reading level. (National Institute of Mental Health) The CD22 study is much more complicated than the study the National Institute of Mental Health uses in their video, so this is more difficult. Some knowledge of leukemia is helpful but not necessary for reading this consent form, which seems reasonable for a study designed for recurrent or resistant disease rather than new patients. While it assumes knowledge of certain terms like apheresis and lymphocytes, newer and more complicated ones that patients previously may not have been exposed to are clearly explained. The capitalization and underlining used in "Chimeric Antigen Receptor (CAR)" is a nice touch because the acronym is crucial.

Overall, this consent form checks all the boxes for an ethical informed consent form. Dr. Fry does a thorough job of ensuring that patients understand that this is a phase one study, the first test on humans, and therefore the side effects are somewhat uncertain. The study is

primarily for research, though patients may see a reduction in disease levels. Patient privacy is also addressed. In conversation, Dr. Fry discussed the difficulty of finding a balance between including everything that is required and keeping the document short enough that patients will read it in detail in order to truly understand it. Although the form ended up filling 20 pages, the simple language and effective use of underlined and italicized text to clarify important ideas made a complicated process much easier to understand. This well-designed consent form protects both the researchers and the patients during this breakthrough trial therapy and leaves patients with a fairly good understanding of what to expect in the process.

Works Cited

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