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WMA Conference on the Revision of the Declaration of Helsinki: Research in Resource-Poor Settings

Session 6
Post-trial access and the Declaration of Helsinki (Part B)

19 January 2024
11:15 AM – 12:30 PM
Vatican City

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Agenda

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Topic #	Topic Description	SLIDE #
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Declaration of Helsinki Relevant Provisions

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22. … In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

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Council for International Organizations of Medical Sciences (CIOMS) – 2016

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The Council for International Organizations of Medical Sciences (CIOMS), in collaboration with the World Health Organization (WHO), states in its *International Ethical Guidelines for Biomedical Research Involving Human Subjects* that companies should consider the following:

"Whether, when and how any products or interventions proven by the research to be safe and effective will be made available to subjects after they have completed their participation in the research, and whether they will be expected to pay for them…"

Reference:
Post-Trial Access to Treatment: How Expanded Access May Offer A Strategic Solution (mytomorrows.com)

Author: Dennis Akkaya, September 2, 2020

"Post-trial availability for communities and populations. Even if research addresses a question that has social value for the community or population where it is carried out, the community or population will not benefit from successful research unless the knowledge and interventions that it produces are made available to them and products are reasonably priced. Post-trial access plans are of particular concern for research conducted in low-resource settings where governments lack the means or infrastructure to make such products widely available."

Human Research Protection Program https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf

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Council for International Organizations of Medical Sciences (CIOMS) - 2016

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Consultation with relevant stakeholders. The obligation to care for participants' health needs rests with the researcher and the sponsor. However, the delivery of care may involve other parties, for example, local health authorities, insurance companies, members of the communities from which participants are drawn, or nongovernmental organizations such as health advocacy groups. Researchers and sponsors must describe their provisions for continued care in the study protocol and show that any other parties involved in continued care have agreed to the plan. Research ethics committees must determine whether the arrangements for continued care are adequate.

Decisions on how to fulfil the obligation to provide transition to care are best made for each study through a transparent and participatory process that involves all relevant stakeholders before the study begins (see Guideline 7 – Community engagement). This process must explore options and determine the core obligations in the particular situation with regard to the level, scope, and duration of any post-trial care and treatment package; equitable access to services; and the responsibility for provision of services. Agreements on who will finance, deliver, and monitor care and treatment must be documented.

Information to participants. Participants must be informed before the trial how the transition to care after research is arranged and to what extent they will be able to receive beneficial study interventions post-trial. Participants who receive continued access before regulatory approval must be informed about the risks of receiving unregistered interventions. When participants are informed about the extent of ancillary care, if any, to be provided, this information should be clearly separated from information about the study interventions and research procedures.

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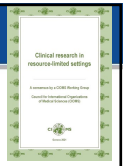
Council for International Organizations of Medical Sciences (CIOMS) – 2021



4.2.3 Caring for participants' health needs

Researchers have an ethical obligation to care for participants' health needs during research and, if necessary, for the transition of participants to care when the research is concluded. Even though such care may be an incentive for participants in low-

resource settings, it should not be considered an undue influence.[1, Guideline 6] In addition, clinical trials sponsors, researchers and host country governments should make provisions for post-trial access to an intervention identified as beneficial in the trial for all participants who still need it. This information must also be disclosed to participants during the informed consent process.[16]

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Council for International Organizations of Medical Sciences (CIOMS) – 2021

Post-trial access to interventions

Information gained from clinical trials conducted efficiently and expeditiously may allow early registration of drugs in LMICs, thus considerably enhancing profits for sponsors. It does not seem irrational to expect them to share these benefits with the research participants in LMICs by continuing to provide them with a proven treatment after the completion of the trial. The provisions for continued care should be described in the study protocol. Sponsors and researchers may no longer have an obligation to provide continued access when the intervention becomes available in the public health system. Moreover, sponsors, researchers and community members may agree before a trial starts that any intervention that has demonstrated significant benefit will be provided only for a predetermined period of time. [1, Guideline 6]

Post-trial access to other benefits

According to the Declaration of Helsinki, "*At the conclusion of the study, patients entered into the study are entitled to... share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits*".[16] There may be cases when the participants ultimately do not gain access to the study intervention, even if the company has had it approved and commercialized. In such cases there should be a system whereby participants in low-resource settings derive some other benefit, for example continued access to an established effective intervention that was provided as part of the standard of care or prevention to all participants during the research. [1, Guideline 6]

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Good Clinical Practice (E6 R2) Yale

ICH harmonisation for better health

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

Does not include language related to Post Trial Access.

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Sponsor Policies

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- Many sponsors have developed policies in regard to access to investigational products, including Post Trial Access. (See Attachment for examples.)
- Depending on the type of study, sponsors often cite to the Declaration of Helsinki and whether investigational products will or will not be available post trial in study protocols.
- Consent forms may also include language regarding what will happen at the end of the study and may specifically address post trial access.

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Ethical Considerations-Belmont Report - 1979

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The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

Respect for Persons	Beneficence	Justice
Potential research participants must have the freedom to make voluntary decisions regarding whether or not to participate in research without coercion or undue influence from others.	The proposed research must be designed to maximize benefits and minimize harms.	The third principle requires the equitable selection of research participants and research that is designed so that the benefits and burdens are shared equitably.
❑ Participants voluntarily consent to participate in the research. ❑ Privacy and Confidentiality are protected. ❑ Participants have the right to withdraw from research. *YouTube: The Belmont Report Dr. Bob Levine* http://www.youtube.com/watch?v=iD-YCDE_5vw	❑ The risks of research are justified by potential benefits to the individual or society. ❑ The study is designed so risks are minimized, and benefits are maximized. ❑ Conflicts of interest are managed adequately.	❑ **Individual Justice-** Should not offer potentially beneficial research or opportunities to some individuals OR exploit certain populations. ❑ **Social Justice** - Equitable selection of research participants is required (participants who may benefit from participation not be excluded without good cause).

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Ethical Considerations-Beauchamp and Childress

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Tom Beauchamp and Jim Childress identify four principles that form a commonly held set of pillars for moral life.

Respect for Persons/Autonomy	Acknowledge a person's right to make choices, to hold views, and to take actions based on personal values and beliefs
Justice	Treat others equitably, distribute benefits/burdens fairly.
Nonmaleficence (do no harm)	Obligation not to inflict harm intentionally; In medical ethics, the physician's guiding maxim is "First, do no harm."
Beneficence (do good)	Provide benefits to persons and contribute to their welfare. Refers to an action done for the benefit of others.

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Ethics Review Approval

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Ethics Committees do not uniformly address Post Trial access in their review of studies.

Example

1. **Continuation of Drug Therapy After Study Closure** ☐**Not applicable to this project**
   Are subjects provided the opportunity to continue to receive the study drug(s) after the study has ended?

☐ **Yes** If yes, describe the conditions under which continued access to study drug(s) may apply as well as conditions for termination of such access. *Write here*

☐ **NO** If no, explain why this is acceptable. *Write here*

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Therapeutic Use of Investigational Drugs

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There is no Common Global Definition or Approach

REVIEW Open Access

Expanded Access Programme: looking for a common definition

Antonella Iudicello[1], Lucia Alberghini[2*], Giulia Benini[2] and Paola Mosconi[3]

Abstract

Therapeutic use of an unauthorised drug (or of an authorised drug for an unauthorised indication) for patients with a life-threating disease is permitted outside a clinical trial as an Expanded Access Programme (EAP).
The regulations regarding EAPs is not the same all over the world. For example, the recommendation of the European Medicines Agency (EMA) in EU countries also includes within EAPs patients who have been treated in a clinical trial and who wish to continue the treatment. Nevertheless, the patients treated in a clinical trial could have the option of continuing treatment for an extended period in an Open-label Extension study, aimed to generate long-term data on efficacy, safety, tolerability and administration.
The aims of this paper – based on the difficulties and incoherence encountered by an Italian Ethic Committee (EC) during the authorisation process of EAPs – are: understanding the origin of this misclassification by analysing differences and similarities among USA, European and Italian regulations concerning EAPs; and showing difficulties in classifying international study protocols as a consequence of the lack of harmonisation of definitions.
We performed a critical review of the current USA, European and Italian regulations and we analysed some practical cases by retrieving protocols from Clinicaltrials.gov and the Italian Clinical Trials Registry (OsSC) containing in the title the keywords 'Expanded Access Programme', "Expanded Access', 'Open-label Extension study' or 'Early Access'.
We observed that the Food and Drug Administration (FDA) definition of EAP is very clear while the EMA definition is similar to that of an Open-label Extension study. This lack of a clear definition generates misclassification and it is possible to find an EAP with an efficacy or safety endpoint; or an EAP managed as a clinical trial; or an EAP classified in Clinical Trials Registries as a phase II, III or IV clinical trial.
The internationalisation of the studies requires a harmonisation on a global level of legislation and definitions to eliminate misclassification of protocols. For this reason, the authors suggest that: a) the EMA definition should be harmonised with the FDA definition of EAPs, b) European regulation, even if optional, should be adopted in a compulsory way by national regulations. Moreover, separate registries for both EAPs and clinical trials should be organised.

Keywords: Expanded access programme, Compassionate use programme, Open-label extension study, Early access programme, Clinical trial

Reference:
Post-Trial Access to Treatment: How Expanded Access May Offer A Strategic Solution (mytomorrows.com)

Author: Dennis Akkaya, September 2, 2020

Open-label extension studies, Long-Term extension studies Post-Trial Access, Treatment Arms, Rollover study Clinical Trials and Phase 4 studies

Many country-specific regulations, including the U.S., do not explicitly address Post-Trial Access (PTA). As a result, PTA is often managed in open-label (OLE), long term/extension (LTE) studies, treatment arms of Clinical Trials, and more recently, Expanded Access Programs which have become the preferred choice.

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Post Trial Access – No Global Definition

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Examples

- Brazil
- Kenya
- South Africa
- Japan
- Canda
- European Medicines Agency
- United States

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Local Requirements

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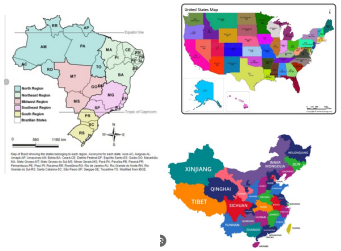
International Compilation of Human Research Standards

See International Compilation of Research Standards located on the HHS website: http://www.hhs.gov/ohrp/international/index.html.

There are also local requirements within jurisdictions in a country requirements



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Post Trial Access – Brazil

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Brazil > Sponsorship > Insurance & Compensation

Last content review/update: April 11, 2023

… As specified in ResNo466 and the G-ClinResSubjectRts , compensation to participants is only provided for transportation costs and meals for the participants and/or their legal representative(s) or guardian(s) during the trial. Post-Trial **Access** According to ResNo563 , for protocols involving research participants diagnosed with ultra-rare diseases, the sponsor must ensure free **access** to the best prophylactic, diagnostic, and therapeutic methods that have proven to be effective at the end of the study, for a period of five (5) years after obtaining National Health Surveillance Agency (Agência Nacional de Vigilância Sanitária (ANVISA)) registration. In addition, per ResNo466 , at the end of the study, the sponsor much ensure free and indefinite **access** to the best prophylactic, diagnostic, and therapeutic methods that have proven to be effective. **Access** must also be guaranteed to participants between the time they stop their participation in the trial and the end of the study. …

https://clinregs.niaid.nih.gov/

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Kenya

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Kenya > Sponsorship > Insurance & Compensation

Last content review/update: March 03, 2023

… Insurance As set forth in the G-KenyaCT and the G-ECBiomedRes , the sponsor must provide insurance cover for the study participants and ensure that the clinical **trial** institution, contract research organization (CRO), and researchers have sufficient insurance cover for the clinical **trial**. Per the G-KenyaCT , the sponsor's policies and procedures should address the costs of treatment of **trial** participants … available to them in the event of **trial**-related injuries. **Trial** Participation The G-ECBiomedRes defines compensation to include offers to participants, monetary or otherwise, to offset the time and inconvenience for participating in research. **Post-Trial Access** Per the G-KenyaCT , the sponsor must put in place measures to ensure that the study participants have **access** to successful investigational products for their disease condition before the products have received a marketing authorization in …

https://clinregs.niaid.nih.gov/

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South Africa

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South Africa > Sponsorship > Insurance & Compensation

Last content review/update: December 18, 2023

… Insurance As set forth in the G-Insurance and the SA-GCPs , all clinical **trial** sponsors and investigators must obtain adequate insurance and indemnity to cover any liability claims during the conduct of a clinical **trial**, in accordance with the responsibilities described in the SA-GCPs . As delineated in the SA-GCPs and … and the SAHPRA reserves the right to request any additional information. In addition, G-TIECompensation is not applicable to Phase I clinical trials, which pose a higher risk for participants and should be compensated on a different scale. **Post-Trial Access** The G-PostCTAccess guides sponsors on when to consider **post-trial** or continued **access** (PTA/CA) to the IP following the **trial**'s conclusion. Only those participants who derive benefit from the IP will be considered (this excludes participants …

https://clinregs.niaid.nih.gov/

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Japan

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Compassionate use (CU) is a system that allows unapproved investigational drugs to be used on a case-by-case basis to treat serious life-threatening diseases for which existing drugs are ineffective from an ethical or humane perspective.[7] CU generally requires several unique conditions to be met. Implementation in public systems, such as laws, and the exceptional use of unapproved investigational drugs under specific conditions are among the prerequisites. Furthermore, patients with specific issues, such as those with serious or life-threatening diseases, those unable to participate in clinical trials, those for whom no approved alternative drugs are available, and those whose self-pay burden is not increased, are included in the prerequisites.[8] In CU, it is also critical that patients' access to unapproved investigational drugs does not interfere with the standard clinical trial process required to approve the drugs.[9] Other terms for "CU" include "Managed Access," "Expanded Access," "Named Patient Supply," "Special Access," "Early Access," and "Temporary Authorization for Use," which are regulations regarding access to investigational drug use for unapproved medicines.[10]

Characteristics of the Compassionate Use Program in Japan: An Analysis of Expanded Access Clinical Trials from 2016 to 2021 - PMC (nih.gov)

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European Medicines Agency (EMA)

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Compassionate use | European Medicines Agency (europa.eu)

The European Medicines Agency (EMA) **provides recommendations** through the Committee for Medicinal Products for Human Use (CHMP), but these do not create a legal framework. Compassionate use programmes are coordinated and implemented by Member States, which set their own rules and procedures.

Established by Article 83 of Regulation (EC) No 726/2004, this tool is designed to:

- facilitate and improve access to compassionate use programmes by patients in the EU;
- favour a common approach regarding the conditions of use, the conditions for distribution and the patients targeted for the compassionate use of unauthorised new medicines;
- increase transparency between Member States in terms of treatment availability.

These programmes are only put in place if the medicine is expected to help patients with **life-threatening, long-lasting or seriously debilitating illnesses**, which cannot be treated satisfactorily with any currently authorised medicine.

The medicine must be undergoing clinical trials or have entered the marketing-authorisation application process and while early studies will generally have been completed, its safety profile and dosage guidelines may not be fully established.

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Options for Access to Investigational Drugs

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There are several mechanisms to obtain access to investigational drugs:

- Post Trial Access
- Expanded Access / Special Access
- Managed Access
- "Right to Try" or equivalent law, etc.
- "[O]pen-label trial extension studies, long-term extension studies, rollover clinical studies, separate protocols, or protocol amendments" (Post-Trial Access to Treatment: How Expanded Access May Offer A Strategic Solution (mytomorrows.com))
- Phase IV Study

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Study Example: Post Trial Access (Access Not Provided)

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Protocol Language

The program will be completed according to the guidelines of Good Clinical Practice. Compliance with this standard provides public assurance that the rights, safety, and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki.

16.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICHGCP, applicable regulatory requirements, and Sponsor's policy on Bioethics.

Consent Form Language

What happens when this study stops?

When the study stops, you will be under the care of your primary doctor who will decide the best way to treat your TS. The study drug will no longer be available to you. About 30 days after the last study drug dose (about 2 weeks after the second follow-up visit), you will receive a phone call from the clinic to follow up on how you are feeling after the study.

You have the right to be informed of the overall results of the study.

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Study Example: Post Trial Access (Access Provided)

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Protocol

6.8. Study Intervention after the End of the Study

Patients receiving clinical benefit from avutometinib ± defactinib may continue receiving treatment until either the final analysis of the ORR endpoint has been completed or all active patients have been followed for 1 year after entry of the last patient, whichever is later. If the study is ended before all patients discontinue treatment, any patient continuing to receive benefit will be provided the opportunity to continue to receive study intervention(s).

Consent Form

What happens after I finish taking the study drug?

You will be able to continue study treatment for as long as you are benefiting from taking the study drug. Reasons for stopping your study treatment early may include growth of your cancer, an unacceptable side effect or because you decide to no longer participate in the study.

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Study Example: Post Trial Access (dependent on local regulation)

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Protocol

6.6 CONTINUED ACCESS TO INTERVENTION AFTER THE END OF THE STUDY

Continued access to the study intervention after the end of the study will be handled according to the local regulations.

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Post Trial Access and Expanded Access-U.S. FDA Yale

FDA Issues Statement on Post-Trial Treatment via Expanded Access | Early Access Care

FDA-Press_PTA_29Mar2019.pdf (earlyaccesscare.com)

What are the different types of expanded access?

1. Expanded access for individual patients, including for emergency use
2. Expanded access for intermediate-size patient groups
3. Expanded access for widespread treatment use

Learn more about expanded access categories for investigational drugs and biologics.

Learn more about expanded access categories for investigational medical devices.

Additional Information on emergency use expanded access:

- FDA may authorize expanded access to an investigational drug or biologic for an individual patient by phone before you submit the written request, or may not object to such investigational use for devices without prior notification, if there is an emergency that requires the patient to be treated.
- For drugs and biologics, emergency requests can be submitted over the phone or other forms of rapid communication (e.g., e-mail) by a licensed physician after receiving agreement from industry to provide the investigational medical product for expanded access use.
- If you have determined that an emergency exists, please follow the instructions on FDA's Expanded Access Contact Information.

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Study Examples – Expanded Access Yale

- Single Patient Expanded Access Program for X unapproved drug in Patients with Compulsive Disorder
- Intermediate Size Expanded Access Program for X unapproved drug in Patients with Multiple Myeloma
- Expanded Access Program of Ruxolitinib for the Emergency Treatment of Cytokine Storm From COVID-19 Infection

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Study Example – Expanded Access

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2000025530: Post Trial Access to Idasanutlin for Treatment of Metastatic Dedifferentiated Liposarcoma

Protocol

2.0 Use Request

Describe the eligibility criteria, usual treatment history for a patient who would qualify for use of the drug or device, the reason use of the drug or device is worth the risk to the patient at this time, and the procedures and methods that the patient(s) will undergo. Indicate if this access is for a single patient, an intermediate size patient population, or widespread treatment use.

This is a single patient expanded access protocol for the treatment of a patient who has done well on the investigational drug idasanutlin but is no longer eligible for the clinical trial. The patient is a 78-year-old man diagnosed with metastatic dedifferentiated liposarcoma. He has received 10 previous cycles of the investigational drug idasanutlin and showed a positive response and clinical benefit. At the current dose and schedule, the patient is doing well and not experiencing toxicity. Continuing benefit is expected. The patient has participated in the clinical trial (HIC 2000022316 "A Phase I Study of New Idasanutlin Tablet Variations in Patients with Solid Tumors) and has completed all eligible treatment under the clinical trial and is no longer eligible for the trial. This is not a research protocol.

Consent Form

The purpose of this form is to explain your options for treatment with an investigational drug or device. Investigational means that the Food and Drug Administration (FDA) has not yet approved the drug or device. Although the safety and effectiveness of the drug or device are not yet proven through clinical trials, you will be given this drug or device to treat your condition. This type of use of an investigational drug or device is known as an *Expanded Access*.

This consent form applies to the use of idasanutlin.

You do not have to agree to this treatment. If we learn something new that may affect the risks or benefits of treatment or your decision to be treated, you will be told as soon as possible.

1. What treatment is being offered?

You are being told about this treatment because you were identified as a possible participant in this program because you have metastatic dedifferentiated liposarcoma, and you no longer respond to, or are unable to take, standard treatments. This drug has not received approval for use in treating your condition from the Food and Drug Administration (FDA). Research studies to see how safe and how well this drug treats diseases may be happening, but you are getting this to treat your condition. You are not receiving this drug for research or as part of a research study at Yale.

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Study Example – Managed Access

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Title: Managed Access Program (MAP) to provide access to tisagenlecleucel in line with locally approved indications, with out of specification leukapheresis product and/or manufactured tisagenlecleucel out of specification for commercial release

Purpose and Conduct

You are being asked to take part in this Managed Access Program because you previously agreed to receive an approved drug, tisagenlecleucel (Kymriah), for the treatment of your disease as part of routine care. You had the blood collection procedure, your T cells were isolated and genetically modified in a laboratory. However, the T cells that were produced do not meet all the pre-specified release criteria to be used as a routine prescription (commercial) drug as required by the FDA.

By participating in this MAP, you will be able to receive tisagenlecleucel even though it did not meet the FDA release criteria.

- The FDA approved the drug treatment Kymriah CAR-T cell therapy (Tisagenelcleucel) for adults with relapsed or refractory follicular lymphoma.
- Patients are offered the drug and undergo the leukapheresis to collect T-cells to send off for modification with Kymriah.
- The FDA approved the use of the drug as long as the target number of T-Cells can be obtained. But if that target is not reached then the drug cannot be given as approved.
- What was created was an expanded access program to allow the lower number (as long as all other parameters are met) to be infused.
- The MAP also allows enrollment of minors because the treatment offers the chance of cure rather than the chemotherapy and transfusion dependent treatments – relatively few – that are approved.

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Canada - Special Access

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Health "Canada's Special Access Program for drugs (SAP) enables drugs that are not marketed in Canada to be requested by practitioners for the treatment, diagnosis, or prevention of serious or life-threatening conditions when conventional therapies have failed, are unsuitable, or unavailable. Non-marketed drugs may be unauthorized if they have not been approved by Health Canada. This means they have not been assessed for safety, effectiveness and quality. It may also mean that the sale of the drug has not commenced in Canada, or the product has been discontinued or removed from the market due to regulatory actions under the *Food and Drug Regulations* (FDR).

The SAP administers the sale[Footnote1] of these drugs for "emergency treatment" under Part C Division 8 of the FDR. An authorization for the sale of drugs that are not available on the Canadian market is based on sufficient evidence supporting the requested use and the drug information available to the SAP at the time of the request.

Special Access Program for drugs: Guidance document for industry and practitioners - Canada.ca

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Study Example – Open Label Extension

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Bepranemab for Prodromal or Mild Alzheimer's Disease

"Bepranemab (UCB0107) is a monoclonal antibody targeting the mid-domain of the tau peptide that is being developed to block and reduce the cell-to-cell spread of tau pathology. This is a Phase 2, double-blind, placebo-controlled study designed to evaluate the safety, tolerability, and efficacy of bepranemab in individuals with prodromal or mild Alzheimer's disease. Participants will be randomly assigned in a 1:1:1 ratio to receive bepranemab at one of two active doses or placebo, administered intravenously every 4 weeks for up to 80 weeks (67% chance of receiving active study drug). All participants will undergo either a 18F-Florbetapir PET scan or a lumbar puncture (as part of an optional CSF substudy) to confirm the presence of cerebral Aβ accumulation. All participants will also receive 4 MRI scans and 3 18F-GTP1 tau PET scans. …

Participants will have the option of continuing in an open-label extension period after completion of the double-blind treatment period. Permits concurrent treatment with cholinesterase inhibitors and memantine. HIC# 2000031213"

Reference: Clinical Trials < Alzheimer's Disease Research Unit (yale.edu)

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Study Example – Behavioral Clinical Trial

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Use of Cognitive-behavioral Therapy (CBT) for Binge Eating (Self-Help Test)

Protocol Language

6.12 Study Completion

The study will be considered complete after all enrolled participants have either completed treatment and their post-evaluation interview or have been withdrawn from/dropped out of treatment (see above for reasons to withdraw participants). Once the study has been completed, researchers will inform the IRB of the change in study status.

There is a chance that participants' eating concerns and overweight may fail to improve or may worsen during the study. Participants will be withdrawn from the study if their clinical condition deteriorates to a significant degree, and they will be provided with appropriate referrals. See below for additional mitigation of risk of worsening.

Procedures for providing follow up care: Study participant safety will be monitored by the study team and reported to the PI at all clinical and assessment visits and referrals will be provided if warranted and/or requested. If a study participant experiences any psychiatric symptoms or distress (e.g., depressive symptoms or suicidality) at any stage of study participation they will receive short-term treatment and support from the study treatment team (which includes psychologists) and will be connected to a local emergency department and their pediatrician or therapist for ongoing care.

- **Total involvement 5 months.**
- **There is a plan if there is no improvement or worsening of condition.**
- **There is no plan in the protocol for referral at end of treatment.**
- **There is also no consideration for the need to continue treatment or provide access through referrals at the end of this feasibility study.**
- **There is no end of treatment assessment.**

OUTCOME

IRB required IRB to provide access.

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Comparison

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Study type	Open-Label Expansion Study	Post-Trial Access (Under Expanded Access)	Phase IV Study
Purpose	Research focused - either standalone or adding treatment arm	Treatment purpose	Research focus
Target population	Confined group	Potentially non-confined group	Large group
Treatment History	Often treatment naive	Up to sponsor – can be more inclusive	Up to sponsor – can be more inclusive
Monitoring	Heavy monitoring	Remote monitoring & occasional on-site follow-up	Remote monitoring (if applied)
Data collection	Large # of tests, assessment and data requirements	Treatment related tests of assessment or standard of care	Minimal data collection
Infrastructure	Heavy research focused set-up	Data that is treatment related, often in patient care setting	Minimum requirements
Set-up times	Lengthy	Shorter than OLE	Shorter than CT
Costs	$$$$$	$$	$$$

Comparison table between Open-Label Extension Study, Post-Trial Access (Under EA) and Phase IV Study

Are there different considerations for research conducted in resource limited settings in regard to Post Trial Access OR Access to Investigational Products in general?

Reference:
Post-Trial Access to Treatment: How Expanded Access May Offer A Strategic Solution (mytomorrows.com)

Author: Dennis Akkaya, September 2, 2020

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Post Trial Access Decision Tree

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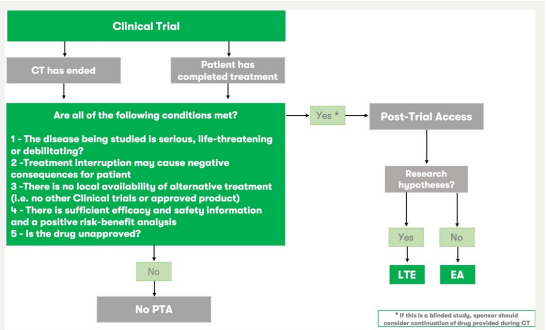

Post-Trial Access Decision Tree

Reference:
Post-Trial Access to Treatment: How Expanded Access May Offer A Strategic Solution (mytomorrows.com)

Author: Dennis Akkaya, September 2, 2020

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Access to Investigational Products – Scenarios

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1. Access to IP for individuals who are not a part of clinical trial
2. Access to IP for individuals who meet inclusion/exclusion criteria, but cannot be in a clinical trial (e.g., due to time commitment, distance, etc.)
3. Access to IP post trial, including early termination.

Possible revision to the Declaration of Helsinki to include guidelines that address each of the scenarios above.

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Considerations

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Considering the scenarios outlined on the previous slide, what are the similarities and differences in regard to impact for the following:

- Global
- Global North versus Global South
- Continent/Region
- Country
- Regions within countries

The answer to this question will help inform possible revisions to the Declaration of Helsinki and applicable guidelines.

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Acknowledgments

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The presenter would like to thank the following colleagues for their contribution to this presentation content.

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