# Yale University
# Human Research Protection Program (HRPP)

## Supplemental Guidance Manual

Version Date: April 3, 2023

**Scope:**

This Supplemental Guidance Manual contains standalone Yale Human Research Protection Program (HRPP) guidance documents, previously published on the Yale HRPP website, that address topics in human research protections in addition to material referenced in other HRPP manuals.

This manual will be periodically updated to include timely and helpful guidance for the research community as the Yale HRPP becomes aware of new information and best practices relevant to the conduct of human subjects research.

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## 330 GD. 1 Reproductive Risks and Contraception in Human Research

### Overview

This guidance addresses the importance of informing research participants about known, possible, or unknown reproductive risks that may affect their decision to participate in the research. Specific issues to discuss with participants are provided below.

### Reproductive Risks: Considerations

Women of childbearing potential who are prospective study participants should be warned about possible and/or unknown reproductive or lactation risks from study treatments. Investigators must discuss these risks and the steps taken to minimize them in both the consent form and in the protocol application.

The general discussion that follows is adapted from a more specific discussion in the **NIH Guidance on Informed Consent for Gene Transfer Research: Reproductive Considerations** (https://osp.od.nih.gov/wp-content/uploads/2014/10/IC2013.pdf). In particular, investigators should consider:

#### *1. Study Specific Harms and Mitigation*

Discussions of reproductive harm, and measures taken to minimize harm, should be study-specific. Factors to be considered include:

- Direct teratogenic effects
- Possible germline effects
- Effects on a woman's ability to continue the current pregnancy
- Effects on fertility and future pregnancies

#### *2. Gender Effects*

Known and unknown reproductive harms and the steps to be taken to avoid or minimize them may be unique to one gender or may be different for men and women. Consent forms and the protocol should be written to address concerns appropriate to each subject population involved in the study.

#### *3. Exclusion and Testing*

While some risks legitimately justify exclusion of particular populations, in many studies prospective subjects have the right to make their own choices about the level of risk they will tolerate—after they have been fully informed of the risks and possible benefits of study participation. If exclusion of pregnant women, nursing women, or people who wish to start a pregnancy is justified for a particular study, the application and consent form must explain the reasons for the exclusion and the steps to be taken to avoid problems (such as pregnancy testing) prior to treatment and periodically (including frequency) during the study and the use of contraceptives.

#### *4. Unintended Pregnancy During the Research*

The application and consent documents must discuss what will happen if a study participant or the partner of a participant becomes pregnant. Typically, the participant must contact the investigator, who can then discuss risks and provide counseling about additional steps to be taken. If the researchers will want to monitor any offspring long term, this should be stated in the consent documents. Some studies find it useful to provide special consent forms for participants who become pregnant and wish to continue in the study; the special consent form should discuss risks and any special additional precautions or follow-up.

#### *5. Banking Sperm and Ova*

Where appropriate, researchers should address the advisability of banking sperm and ova, including the likely additional costs for participants.

## Contraception

### *Abstinence and Methods of Contraception*

Methods required by the protocol and described in (or appended to) the consent form should be adequate to address the specific risks of the study.

**The time period** when contraceptive steps should be taken—before, during, or after the research intervention—should be made clear in the application and consent forms.

**Choices of methods** should be as broad as possible and must be consistent with subject safety. Subjects should be told the short- and long-term advantages and disadvantages of the allowable methods.

**Barrier methods** should be used where body fluids may transfer infectious agents, vectors, or medications.

## Sample Consent Form Wording

The sample consent form wording that follows is adapted from the Informed Consent Guidance for Human Gene Transfer Trials subject to the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules. The NIH guidelines include a number of additional examples that will be useful in many different kinds of studies and for both women and men. The wording in any example will need to be adapted to the particular study and subject population.

> **Example 1:** You should not be in this study if you are a pregnant or nursing mother or if you are planning a pregnancy soon. The [*study treatments—name the relevant treatments*] may cause harm to the mother and to unborn or breast-feeding children. You should not become pregnant during the study. If you can give birth or father a child, you must use an adequate form of birth control. If you are able to become pregnant, you must have a negative pregnancy test within [*time*] before you get the first [*treatment*], and you will be tested for pregnancy every [*interval*] during the study. If you become pregnant while in this study, you should tell the study doctor immediately. The study doctor will counsel you about your choices, and, if you decide to stay in the study, will ask you to sign a new consent form so that information about your pregnancy and delivery can be recorded.

> **Example 2:** You should not exchange body fluids with another person after you start the [treatment] and for [time period] after the [treatment] stops. The best way to avoid exchanging fluids is to abstain from sexual activity for the [time period] you are in active treatment. Other less effective ways to avoid exchanging fluids include barrier contraceptive methods such as [specify].

Refer to the Consent Glossary found in the IRES IRB Library (Consent Glossary_Glossary of preferred and required terms for consent forms) for specific language addressing reproductive risks for women and men participating in research at St. Francis and other hospitals within Trinity Health of New England.

## References

**NIH Guidance on Informed Consent for Gene Transfer Research: Reproductive Considerations**
(https://osp.od.nih.gov/wp-content/uploads/2014/10/IC2013.pdf)

## Revision History:

8/28/2012, 9/13/2012, 1/19/2013, 10/17/2022

# Yale University Institutional Review Boards

## 720 GD 2 Depression and Suicidality in Human Research

## Overview

Research studies that include measures for depression and suicidality should anticipate that certain participant responses may necessitate some level of intervention. A plan for how these research findings will be handled, should they arise, should be provided with the IRB protocol. These plans should include the time frame for scoring the measure(s), the participant response thresholds that would prompt further intervention, and details of the planned interventions for differing severities of depression or suicidality, including a plan for how imminent risk of harm will be handled for the study's targeted population (Yale students, other Yale affiliates, or non-Yale community participants). When follow-up interactions or interventions are planned for participant responses surpassing certain thresholds, participants should be informed beforehand that there may be a consequence based on their response. Examples of acceptable plans are described below for handling study findings of depression, suicidal ideation and suicidal intent for two measures commonly used to score for depression in research studies, the Beck Depression Inventory (BDI) and the Structured Clinical Interview (SCID). The investigator is encouraged to formulate a plan that fits the specifics of the study, and the IRB will determine the appropriateness of that plan on a protocol by protocol basis.

The investigator administering the measure should be a qualified, clinically trained graduate student, faculty member or other clinician, or be closely advised by someone with the proper qualifications and training who is available while participants are being administered the measure(s). If the investigator administering the measures does not have appropriate clinical training, he or she should immediately contact a designated, qualified clinician to come to the experimental session and administer a thorough risk assessment for any participants endorsing suicidal ideation. The IRB should be notified as soon as possible, but within 48 hours in cases where imminent risk of harm is determined, or if the rate of depression and/or suicidality is found to be higher than would reasonably be expected in the studied population.

## The Beck Depression Inventory (BDI)

The BDI includes 21 items that assess the severity of depression and is oriented toward the symptoms of depression as described in Diagnostic and Statistical Manual for Mental Disorders – Fifth Edition/Text Revision (DSM-5-TR). The BDI includes a single item that directly assesses suicidal ideation. The scale was developed for use with adults, but has also been used with adolescents. A child-friendly version, known as the Child Depression Inventory (CDI) is used with younger children.

Beck, A. T., Steer, R. A., & Brown, G. K. (1996). Beck Depression Inventory: Second Edition manual. San Antonio: The Psychological Corporation.

### Use of the BDI in Research Studies and Scoring for Depression

Investigators should consider providing information regarding appropriate counseling services to all participants in research studies that involve administering the BDI, regardless of their BDI scores. Study specifics, including the population being targeted and what identifiers will be linked to responses, influence how this may be implemented. For instance, studies involving Yale University students and affiliates should retain a link to identifiers (or justify why this is infeasible) and may refer the students to the Yale Health's Mental Health and Counseling Department. Non-student and community participants can be referred to the Yale Psychology Department Clinic and other local resources. Some studies with community participants can likewise be given contact information for suicide or other appropriate hotlines, with instructions to call these mental health service hotlines if they choose certain answers to specific questions. In Connecticut, Crisis Services are available by calling 2-1-1. Providing all participants with contact information for appropriate resources is particularly encouraged in cases where the investigator is unable to correlate a particular score with a given participant. When specific interactions or interventions are planned for individuals with particular threshold responses, participant contact information should be

maintained and linked to responses until the result of the measure is reasonably known, and the consent form should inform of the possibility that these follow-up interventions may occur based on their responses.

A participant score above a specific pre-defined threshold on the BDI warrants the investigator (or other qualified, clinically-trained study personnel) sharing these study findings with the participant and providing appropriate referrals and assistance in reaching counseling resources. Each item of the BDI is scored from 0 to 3, and scores across all items are totaled for a possible high score of 63. Authors of the BDI (Beck et al., 1996) have established cut-offs for moderate depression (scores of 20-28) and severe depression (scores of 29-63). A 2009 administration of the BDI to Yale Freshman showed that 14 percent of freshmen scored a 20 or higher on the BDI, 8 percent scored above a 25 on the BDI, and 5 percent scored above a 29 or higher on the BDI, which are higher scores on average than the general population (S. Nolen-Hoeksema). Accordingly, a BDI score of 25 – the mid-range of moderate depression – has been recommended as the scoring threshold for personal follow up with student participants; the cut-off for severe depression (29) could miss participants who might need help; and the cut-off for moderate depression (20) could prompt communicating study results and assisting a very large percentage of participants, many of whom are not in need of help. Other populations may warrant a different scoring threshold for intervention, but the threshold should be defined in the application and the rationale for using a different threshold provided.

## Sharing Study Findings with Persons Requiring Follow-Up for Depression

Whenever possible, participants with BDI scores designating them for follow-up should be contacted by a qualified clinician investigator or faculty advisor the same day the BDI is completed. Email is an acceptable means of follow-up, and the following communiqué has been used previously:

- For students or community participants in survey studies in which there is not direct contact with the experimenter (such as with computer-based BDI administration):

  “I am a [investigator / faculty supervisor] of the psychology research study that you recently completed. From your answers to one of the questionnaires, you seemed to be feeling quite down and blue. We provided you with some information about counseling services at the end of the survey, but I wanted to follow-up and offer to provide any other referral information you might want.”

- For students or community participants in face-to-face experiments:

  “I am a [investigator / faculty supervisor] of the psychology experiment you did recently. The person who ran your experiment noticed that you seemed to be feeling quite down and blue, according one of the questionnaires you completed. You were given some information about counseling services on the debriefing sheet, but I wanted to follow-up and offer to provide any other referral information you might want.”

Participants who respond to this email should be encouraged to make an appointment with the Yale Mental Health and Counseling Services (for students), Yale Psychology Department Clinic or other counseling resource as appropriate. Assistance in making appointments should be provided if requested. Those requesting referrals outside the University should be given a list of referrals of therapists who specialize in mood disorders.

## Sharing Study Findings with Persons Requiring Follow-Up for Suicidality

Further precautions are needed for any student or community participant who indicates possible suicidality or imminent harm. In survey studies in which there is not direct contact with the experimenter, any student or community participant who endorses a response of "I would like to kill myself" or "I would kill myself if I had the chance" to the BDI item 9 is contacted by phone or email the same day that the participant provides the data, regardless of the participant’s total score on the BDI. Further determinations should be made by individuals who are clinically qualified to assess these conditions. Should there be signs of imminent risk in subsequent emails or phone contact, a verbal contract to not hurt oneself would be made and directions to the Yale Health Mental Health and Counseling (for students) or Yale-New Haven Hospital (for others) must be given. If the individual does not agree to a verbal contract, the police must be informed to provide for more direct contact with the high-risk individual.

The IRB must be informed in cases where imminent risk of harm is discovered. The consent form must include the possibility that follow-up interventions may be taken based on the participant's responses.

# The Structured Clinical Interview (SCID)

The Structured Clinical Interview (SCID; First, Spitzer, Gibbon & Williams, 1995) comprises multiple modules, each assessing for different classes of diagnoses, and is generally administered in person. The SCID may be administered to assess for current depression; questions for the depression module of the SCID conform to criteria in the DSM-5. Depending on the module given, the SCID can also yield results that would have confidentiality issues such as drug abuse.

First MB, Williams JBW, Karg RS, Spitzer RL: Structured Clinical Interview for DSM-5—Research Version (SCID-5 for DSM-5, Research Version; SCID-5-RV). Arlington, VA, American Psychiatric Association, 2015

## Sharing Study Findings with Persons Requiring Follow-Up for Depression

Referral information for psychological treatment and any additional assistance for participants meeting clinically significant criteria of the SCID for depression should be provided as described above for the BDI.

## Sharing Study Findings with Persons Requiring Follow-Up for Suicidality

In research studies in which the SCID is administered for depression, any participant who endorses suicidal ideation during the structured interview must be given a thorough risk assessment by the experimenter (or their qualified clinically-trained advisor) before leaving the experimental session. Specifically, a positive response to either of the questions, "In the past month, were things so bad that you were thinking a lot about death or that you would be better off dead?" and "What about thinking of hurting yourself?" would prompt further clinical examination. If any participant is actively suicidal, students are taken to Yale Health Mental Health and Counseling or to Yale-New Haven Hospital; non-student and community participants are taken to the Yale Psychology Department Clinic or Yale-New Haven Hospital. Any faculty advisor supervising the study and the IRB monitoring the study must be immediately contacted in such an incident. If the individual does not agree to be taken for additional clinical evaluation, the police must be informed to assist with the high-risk individual. As with the BDI, the IRB must be informed in cases where imminent risk of harm is discovered, and participants should be informed beforehand that follow-up interventions may occur based on their responses.

# Yale University Human Research Protection Program

## Reference Guide
### Blood Limit Guidelines for Adult and Pediatric Research



**Purpose**

This document provides guidelines for assessing whether blood collection for research is appropriate for studies involving adults and/or pediatric populations.

**Scope**

The scope of this document is limited to human subjects research involving the collection of blood samples from research participants. The collection of blood samples that is part of routine standard of care and/or a non-research clinical care procedure is outside of the scope of this document.

***Note**: The content of this document does not supersede the authority of any existing applicable guidance or governing documents. In the event of any conflict between this content and any applicable policy, such applicable policy supersedes.*

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**Overview**

No endeavor designed to collect data from human research subjects is more fundamental than blood sampling. No human tissue is more elemental by nature, responsible for hemostasis and able to test the interplay of science, ethics and law than blood. The foreseeable physiologic consequences of blood collection differ greatly across the spectrum of disease and age. For these reasons, Institutional Review Boards (IRBs) provide guidance to minimize the risks associated with research blood sampling and recognize certain populations may require special protections.

A person's total blood volume (TBV) is related to body weight. The TBV of a child is around 75-80 ml/kg and is higher in the neonatal period.[1] A reasonable figure for calculation of TBV for adults is 70ml/kg of body weight.[2] A loss of blood volume has known physiologic effects on human homeostasis.[3]

Diagnostic phlebotomy has been associated with alterations in hemoglobin and hematocrit levels and has been linked to hospitalized patient morbidity. In one study, diagnostic phlebotomy was shown to contribute to anemia in patients admitted to an internal medicine service.[4] Low hemoglobin and hematocrit levels may result in significant morbidity for patients with underlying cardiorespiratory diseases.[5] Also, previous evidence supports laboratory phlebotomy loss as the primary contributor to anemia in the weeks immediately after birth.[6] Meanwhile, certain disease states such as iron-deficiency and myelodysplastic syndromes can exacerbate the effects of phlebotomy.

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**Guidance Statement**

The collection of blood from human research participants requires attention to foreseeable physiologic consequences that single and aggregate blood collection can impart on research subjects in health and in various disease states. This research must be designed to ensure that the volume, collection technique, and frequency of collection is reasonably calculated to represent no more than physiologic minimal risk to human subjects. Research that includes the collection of blood samples that exceeds these guidelines

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[1] H. Pearson, *Blood and Blood Forming Tissues,* in *21st Edition Rudolph's Pediatrics*, 1521 (Rudolph C, Rudolph A, ed., McGraw-Hill Medical 2003).

[2] *Blood Drawing for Human Subjects Research*, University of Pittsburgh Human Research Protection Office, http://www.irb.pitt.edu/blood-drawings-human-subject-research (last visited Aug. 10, 2020).

[3] Stephen RC Howie, *Blood Sample Volumes in Child Health Research: Review of Safe Limits*, 89, Bulletin of the World Health Organization 46-53 https://www.who.int/bulletin/volumes/89/1/10-080010/en/ (2011).

[4] E. Joosten, et al., *Blood Loss from Diagnostic Laboratory Tests in Elderly Patients*, 40, J Am Geriatric Soc 298 (1992).

[5] Christopher B Arant, et al, *Hemoglobin Level is an Independent Predictor for Adverse Cardiovascular Outcomes in Women Undergoing Evaluation for Chest Pain: Results from the National Heart, Lung, and Blood Institute Women's Ischemia Syndrome Evaluation Study*, 43, J Am Coll Cardiol 2009-2014 (2004).

[6] V S Blanchette & A Zipursky, *Assessment of Anemia in Newborn Infants*, 11 Clin Perinatol 489-516 (1984).

may be approved, provided special safeguards are instituted to mitigate and justify risks to human subjects.

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**Definitions**

**Children**

"Children" are persons who, at the time of enrollment in a research study, have not attained the legal age for consent to treatments or procedures involved in the research under the applicable law of the jurisdiction in which the research will be conducted. 45 C.F.R. §46.402(a); 21 C.F.R. §50.3(o).[7] In the State of Connecticut, the age of majority is 18. Investigators working in locations outside Connecticut should confirm the local age of majority to determine at what age a person is considered to be an adult.

**Infants**

"Infants" are children under 2 years of age.[8]

**Investigator or Principal Investigator (PI)**

"Investigator" refers to an individual performing various tasks related to the conduct of human subjects research activities, such as obtaining informed consent from subjects, interacting with subjects, and communicating with the IRB. Although some research studies are conducted by more than one investigator, usually one investigator is designed the "Principal Investigator (PI)" with overall responsibility to supervise the conduct of the study. When tasks are delegated, the PI is responsible for providing adequate supervision of those to whom tasks are delegated. The PI is also accountable for regulatory violations from failure to adequate supervise the conduct of the study. See, HHS Guidance: Investigator Responsibilities; FDA Guidance: Investigator Responsibilities. When delegating responsibilities PIs should consider whether:

- Individuals who were delegated tasks were qualified to perform such tasks;
- Study staff received adequate training on how to conduct the delegated tasks and were provided with an adequate understanding of the study;
- There was adequate supervision and involvement in the ongoing conduct of the study;
- And there was adequate supervision or oversight of any third parties involved in the conduct of a study to the extent such supervision or oversight was reasonable possible.

**Neonates**

"Neonates" are infants who are newborns. 45 C.F.R. §46.202(d).[9] The World Health Organization provides that newborn infants, or "neonates," are children under 28 days of age. See, who.int/infant-newborn/en/.

**Minimal Risk**

"Minimal risk" means the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. 45 C.F.R. §46.102(j); 21 C.F.R. §50.3(k).[10]

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[7] 45 C.F.R. §46.402(a); 21 C.F.R. §50.3(o)

[8] *Providing Information about Pediatric Uses of Medical Devices,* FDA Guidance for Industry and Food and Drug Administration Staff 3-4, https://www.fda.gov/media/85233/download (May 1, 2014).

[9] 45 C.F.R. §46.202(d)

[10] 45 C.F.R. §46.102(j); 21 C.F.R. §50.3(k)

**Pediatric Patients**
"Pediatric patients" means patients who are 21 years of age or younger (that is, from birth through the twenty-first year of life, up to but not including the twenty-second birthday) at the time of the diagnosis or treatment. See, 21 CFR §814.3(s).

**Phlebotomy**
"Phlebotomy" or "blood sampling" is the act of drawing or removing blood from the circulatory system through a cut (incision) or puncture in order to obtain a sample for analysis and diagnosis.

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**Information Sections**

1. **Minimal Risk Research**
   In some instances, the collection of blood samples may be considered to present no more than minimal risk to research subjects and may be reviewed by an expedited procedure. 45 C.F.R. 46.110; 21 C.F.R. 56.110.[11] Blood sampling, collected by finger stick, heel stick, ear stick or venipuncture, may be reviewed by expedited review under the below-described circumstances.[12] Blood sampling collected by other means, even if it may be considered to be minimal risk and otherwise meets the expedited review criteria, must be reviewed by the convened IRB. Amounts in excess of these limits should be evaluated on a case-by-case basis.

   **1.1 Healthy, Nonpregnant Adults Who Weigh at Least 110 Pounds**
   The amounts drawn for research purposes may not exceed 550 ml in an 8-week period and collection may not occur more frequently than 2 times per week.[13]

   **1.2 Other Adults**
   Blood samples may be collected for research purposes from other adults considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml/kg in an 8-week period and collection may not occur more frequently than 2 times per week.[13]

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[11] 45 C.F.R. 46.110; 21 C.F.R. 56.110

[12] *OHRP Expedited Review Categories (1998),* https://www.hhs.gov/ohrp/regulations-and-policy/guidance/categories-of-research-expedited-review-procedure-1998/index.html

[13] *Blood Drawing for Human Subjects Research*, University of Pittsburgh Human Research Protection Office, http://www.irb.pitt.edu/blood-drawings-human-subject-research (last visited Aug. 10, 2020); *Blood Drawing for Human Subject Research*, Duke University Health System Human Research Protection Program, https://irb.duhs.duke.edu/sites/irb.duhs.duke.edu/files/Blood_Collect_Policy_Statement_12-13-2012.pdf (Dec. 13, 2012); M95-9 (rev.), *Guidelines for Blood Drawn for Research Purposes in the Clinical Center*, NIH Clinical Center, available at Children's Hospital of Philadelphia Research Institute IRB Office, https://irb.research.chop.edu/sites/default/files/documents/g_nih_blooddraws.pdf (June 5, 2009); *Policies & Procedures for the Protection of Human Subjects in Research*, Dana-Farber/Harvard Cancer Center Office for Human Research Studies, https://www.dfhcc.harvard.edu/crs-resources/user_upload/IRB_Policies_and_Procedures_for_the_Protection_of_Human_Subjects.pdf (last visited Aug. 10, 2020); *Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Paediatric Population*, European Union, https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-10/ethical_considerations_en.pdf (2008).

### 1.3 Children, Including Infants and Neonates

The amounts drawn for research purposes may not exceed the lesser of 50 ml or 3 ml/kg in an 8-week period and collection may not occur more frequently than 2 times per week.[13]

## 2. Greater Than Minimal Risk Research Involving Adults

Blood sampling procedures that involve greater than minimal risk (e.g. aggregate volume, clinical context) must undergo review by the convened IRB. Maximum allowable volume (ml) phlebotomy limits are provided for reference.

### 2.1 Healthy, Nonpregnant Adults

The maximum allowable volume (ml) to be collected for both clinical care and research purposes shall be 3% of TBV in a 24-hour period and 10% of TBV in a 30-day period.[14]

### 2.2 Other Adults

The ml to be collected for both clinical care and research purposes shall be 2.5% of TBV in a 24-hour period and 5% of TBV in a 30-day period.[14]

## 3. Greater Than Minimal Risk Research Involving Children

Federal regulations do not allow children to participate in research unless the research involves minimal risk or, if more than minimal risk, the research presents the prospect of direct benefit to the subject. In studies where the direct benefit far outweighs the above limits of 3ml/kg in an 8-week period, a full protocol must be submitted for review by the convened IRB and the following guidelines will apply:

### 3.1 Children

If more than 3 ml/kg body weight in an 8-week period is required and justified by the potential benefits to the subject, up to 9 ml/kg in an 8-week period may be considered in older children, which excludes infants, neonates and toddlers.[15]

The requirement for additional safeguards such as supplemental iron, hemoglobin monitoring, etc. for older children providing blood volume amounts between 3ml/kg and 9ml/kg in an 8-week period will be made by the Principal Investigator (PI) and/or clinical attending of each subject.

### 3.2 Infants and Neonates

Maximum blood limits from infants and neonates will be determined by the convened IRB on a case-by-case basis.

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[14] *Maximum Allowable Blood Draw Volumes*, University of Pennsylvania Institutional Review Board, https://irb.upenn.edu/sites/default/files/Maximum-Blood-Draw%20Limits_Penn.pdf (Jan. 2020).

[15] *Blood Sampling Guidelines*, Mass General Brigham Human Research Protection Program, https://www.massgeneralbrigham.org/sites/default/files/2020-06/Blood-Sampling-Guidelines.pdf (last visited Aug. 10, 2020).

## 4. Maximum Allowable Volume Chart

The following chart summarizes the above information.

| Level of Risk of Research | Subjects | Maximum Allowable Volume (ml) to be Collected | Max Frequency of Collection |
|---|---|---|---|
| Minimal risk | Healthy, nonpregnant adults who weigh at least 110 pounds | 550 ml in an 8-week period | 2 times per week |
| Minimal risk | Other adults | Lesser of 50 ml or 3 ml/kg in an 8-week period | 2 times per week |
| Minimal risk | Children, Including Infants and Neonates | Lesser of 50 ml or 3 ml/kg in an 8-week period | 2 times per week |
| Greater than minimal risk | Healthy, nonpregnant adults | 3% of TBV | 24-hour period |
| Greater than minimal risk | Other adults | 2.5% of TBV<br>5% of TBV | 24-hour period<br>30-day period |
| Greater than minimal risk and direct benefit to subjects | Older children | 3 ml/kg in an 8-week period | |
| Greater than minimal risk and direct benefit to subjects when direct benefit far outweighs limit of 3 ml/kg in an 8-week period | Older children | 9 ml/kg in an 8-week period | |
| Greater than minimal risk | Infants and neonates | Case-by-case | |

## 5. Investigator Responsibilities

The investigator responsibilities include, but are not limited to, the following:

### 5.1 Submission of Materials for IRB Review

The investigator must specifically state the total volume of blood to be drawn, the collection procedure, and the frequency with which blood will be collected where appropriate in all materials submitted for IRB review.

### 5.2 Rationale and Safeguards for Amounts in Excess of Prescribed Limits

If the study protocols require that the volume of blood exceeds the maximum limit criteria prescribed herein, the investigator must 1) provide rationale to justify the requested limit and 2) describe what safeguards are in place to protect subjects from undue risk.

### 5.3 Observance of and Adherence to the IRB's Blood Drawing Determinations

With the initial review of proposed research (Yale HRPP Policy-100 IRB Review), the IRB routinely considers whether the blood collections including volume, frequency, and method of collection and clinical factors are appropriate for the intended population(s).

The investigator is responsible for ensuring observance of and adherence to IRB-approved blood drawing determinations.

## Special Considerations

### IRB Review

The IRB may request any additional information it finds materially related to its assessment and determination regarding proposed research blood sampling of subjects. Based on the information provided, the IRB may apply any additional protection or safeguard it deems appropriate. The IRB also may postpone a protocol for more information, approve with modification, approve with restrictions, or consider any other possible action outlined in 100 PR.1 Review by a Convened IRB.

### Children

All decisions regarding research blood sampling involving children will take into consideration guidance set out in IRB Policy 310 Participation of Children in Research. The volume of blood withdrawn from children should be justified in protocols and both the volume and number of venipunctures should be minimized using approaches that include sensitive assays for parent drugs and metabolites to decrease the volume of blood required per sample, use of laboratories experienced in handling small volumes of blood for pharmacokinetic analyses and for laboratory safety studies, the collection of routine, clinical blood samples wherever possible at the same time as samples are obtained for pharmacokinetic analysis, use of indwelling catheters to minimize distress, and use of population pharmacokinetics and sparse sampling based on optimal sampling theory to minimize the number of samples obtained from each patient.[16]

### Special Populations

Special populations including, but not limited to, early neonates, preterm infants, adolescents and emancipated minors deserve special recognition and may require additional safeguards. Similarly, religion, cultural and local norms may require alteration of phlebotomy volumes previously stated in the above Information Sections.

### Risks and Benefits of Blood Draws for Research Purposes

It is important to take into consideration the following issues when assessing the risks and benefits of blood draws for research purposes:

1. Current health status of the individual (Note: Changes in a subject's clinical condition may necessitate alteration or suspension of previously approved phlebotomy limits for research. Recognizing and monitoring such clinical change, is the responsibility of the investigator and clinical attending when applicable.);
2. Volume of blood withdrawn for clinical care;
3. Withdraw only the minimal amount of blood needed to meet the goals of the particular study;

[16] See, *E11 Clinical Investigation of Medicinal Products in the Pediatric Population*, ICH E11 7-8, https://www.fda.gov/media/71355/download (December 2000); *E11(R1) Addendum: Clinical Investigation of Medicinal Products in the Pediatric Population*, ICH E11(R1) https://www.fda.gov/media/101398/download (April 2018).

4. Obtain research blood at the same time as any clinical labs if possible.[17]

**Contacts**

| Subject | Contact | Telephone |
|---|---|---|
| YU IRB | HRPP@yale.edu | 203-785-4688 |

**Revision History**

| Date | Description of the Revision |
|---|---|
| 01Sept2020 | Effective date |

## [Reserved]

[17] *Blood Drawing for Human Subjects Research*, University of Pittsburgh Human Research Protection Office, http://www.irb.pitt.edu/blood-drawings-human-subject-research (last visited Aug. 10, 2020).