

# **The Role of the IRB in Clinical Trials: What Patients and Families Need to Know**

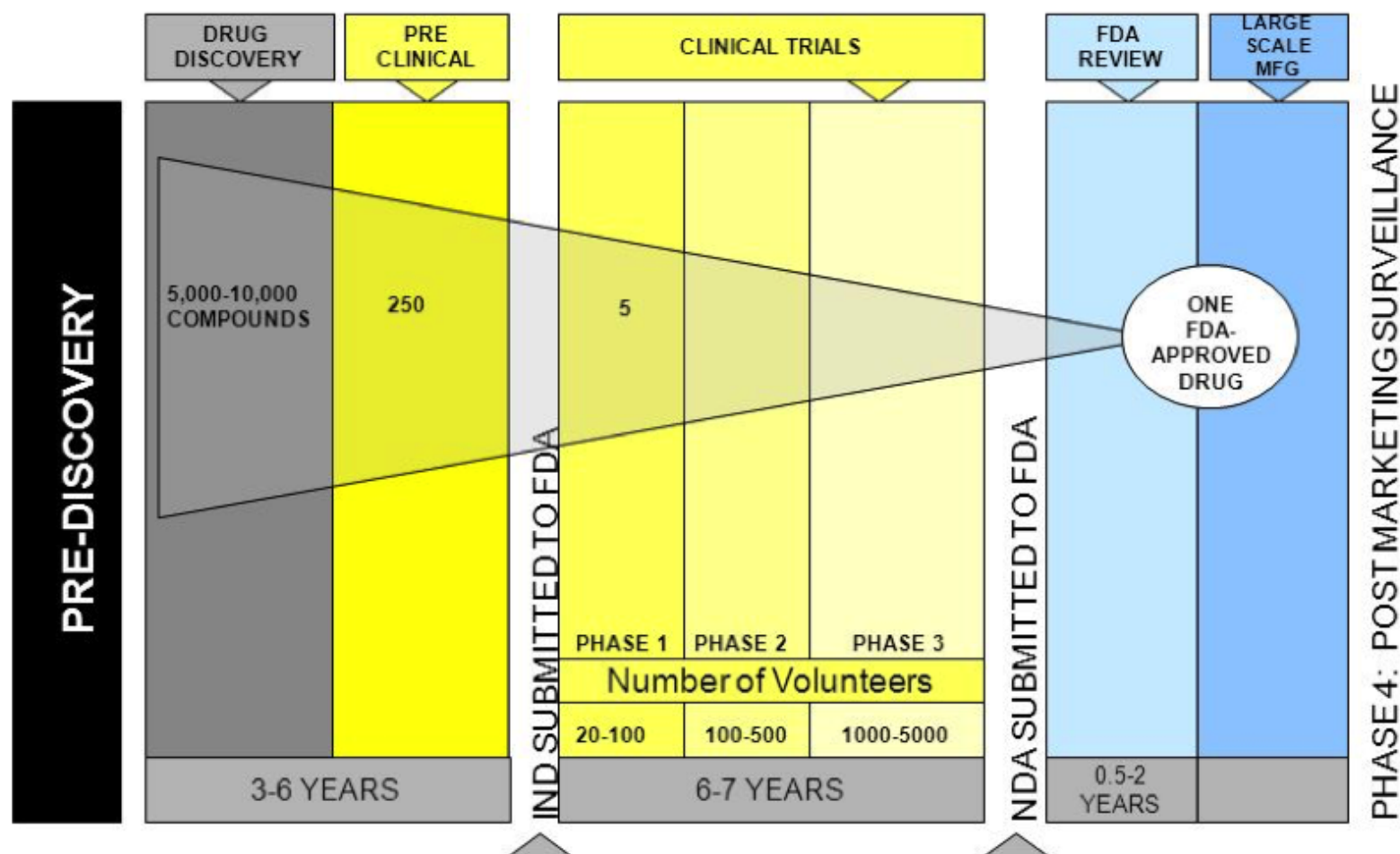
Marjorie A. Speers, Ph.D.  
Executive Director, WCG Foundation



## ! Values

- ❖ Put the children and their families **first** in everything we do
- ❖ Support the members and the childhood cancer community while being mindful not to compete with members or to duplicate projects/programs/services that they provide
- ❖ Be accountable and take ownership of one's commitments within the collaborative
- ❖ Be cost effective with resources
- ❖ Be inclusive and collaborative and assume positive intent
- ❖ Help give voice to the community, and amplify it in a coordinated fashion
- ❖ Stay action-oriented and flexible

# Research and Development Process



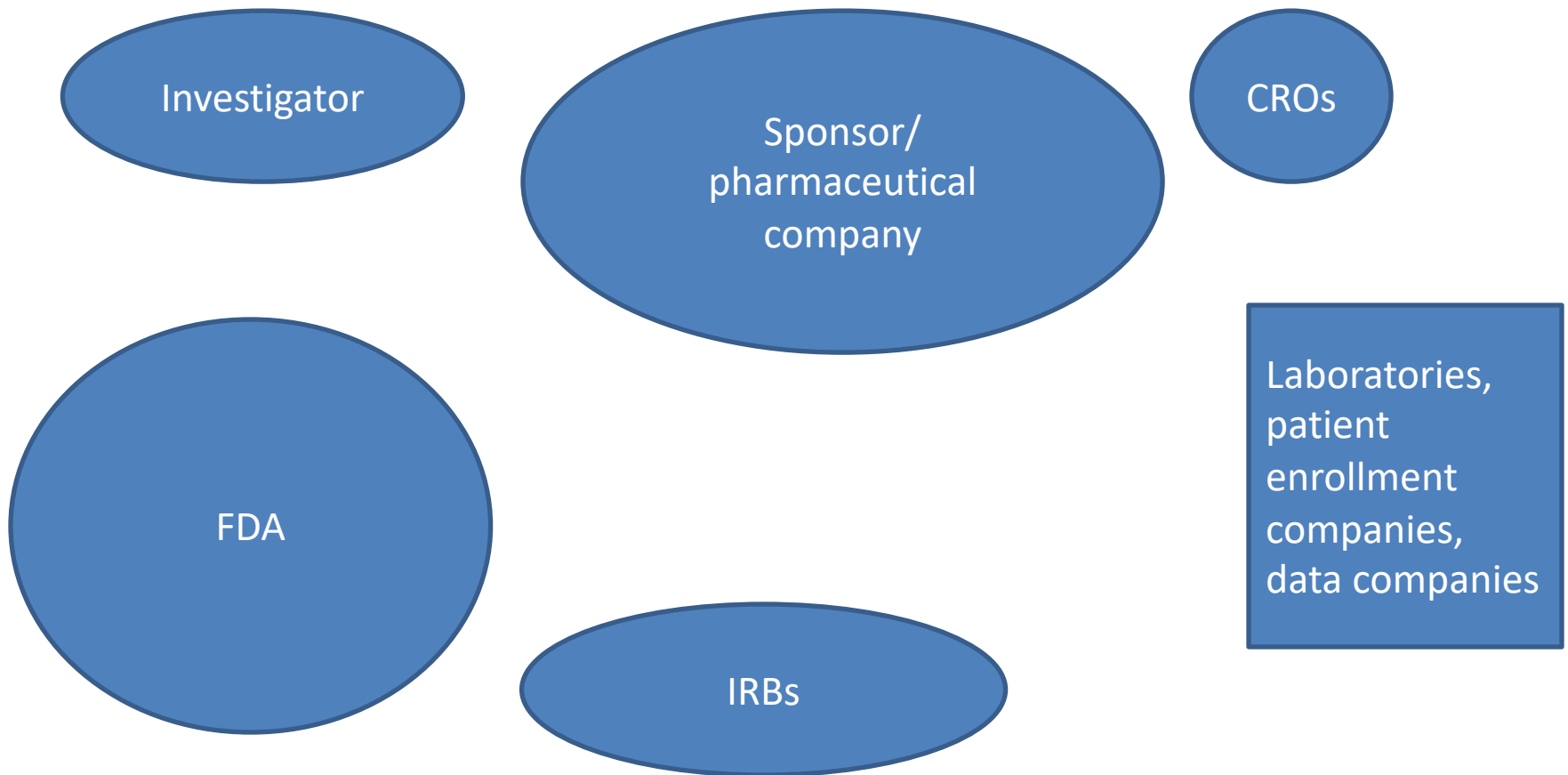
# Phases of Clinical Trials

- Phase 1 – purpose is to determine safety and dosage
- Phase 2 – purpose is to determine efficacy (does it appear to produce the intended outcome) and side effects
- Phase 3 – purpose is to determine efficacy and adverse events
- Phase 4 – (post marketing) purpose is to determine safety and efficacy

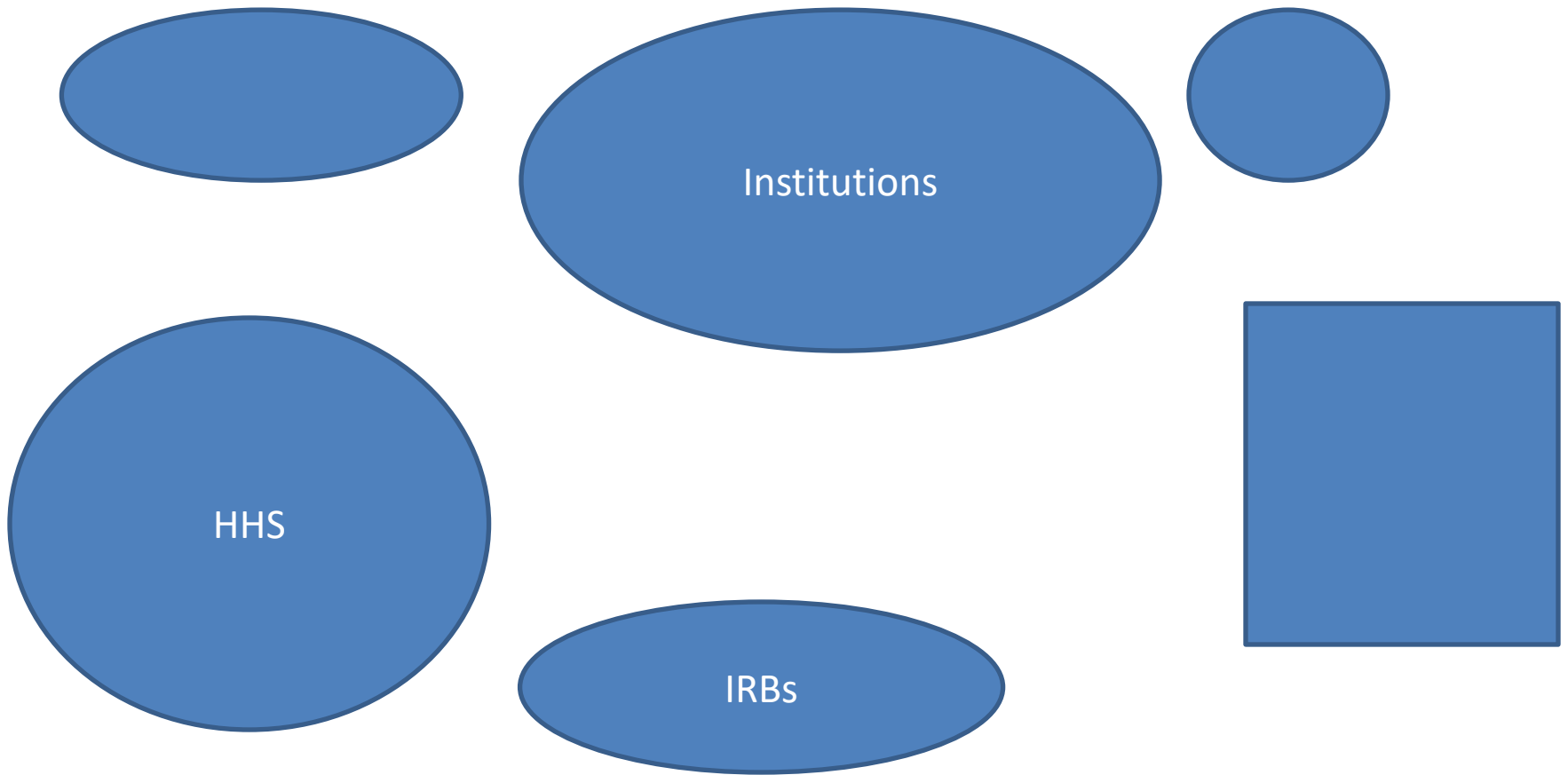
# Phases 1-3 are clinical research (clinical trial, clinical investigation)

- *Clinical investigation* means any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit.
- *Human subject* means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient.

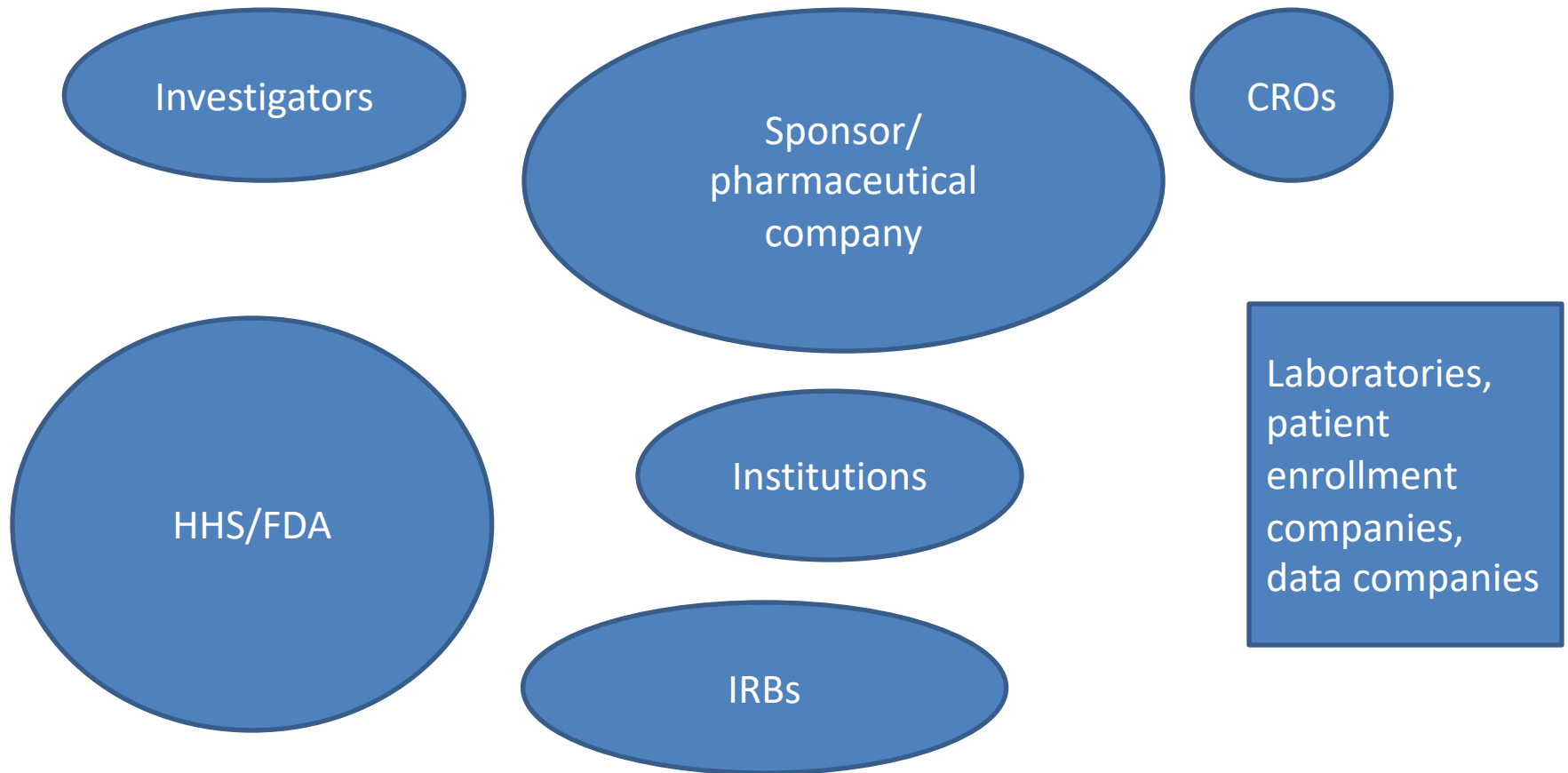
# Many players/stakeholders in FDA-regulated clinical trials



# Many players/stakeholders in NIH-funded research

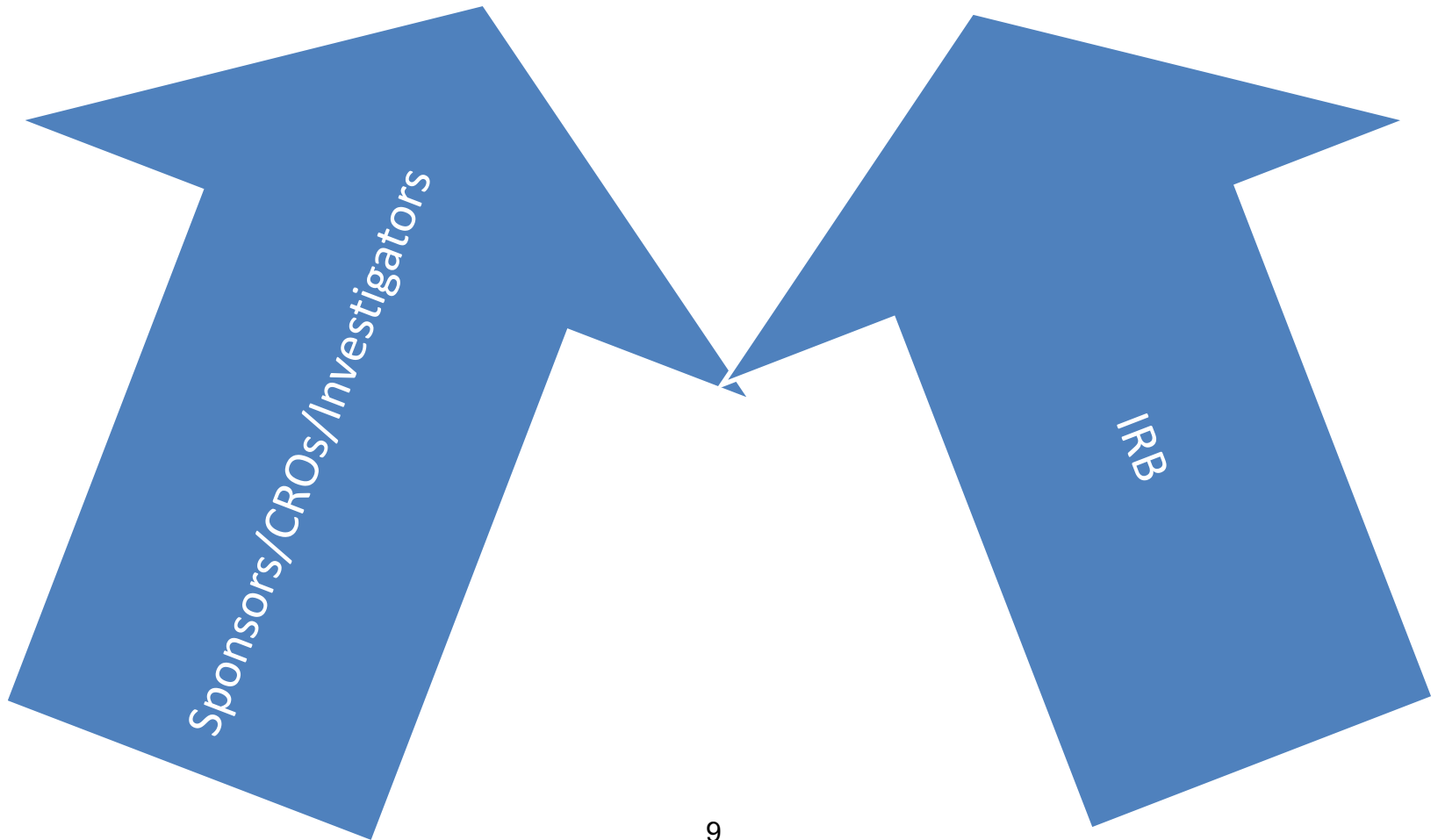


# Many players/stakeholders in FDA and HHS-regulated research





# New medicines to treat patients



# Same goal : different emphasis

- All players share the same goals of excellent, ethically sound science
- Sponsors, CROs, investigators focus primarily on the science
- IRBs focus primarily on protecting human subjects

# What are IRBs?

- First IRB appeared in the 1960's, first at NIH
- Two sets of regulations potentially govern clinical trials (depending on whether the research is federally funded or industry funded)
  - FDA – 21 CFR 50, 56 (apply to research involving test articles)
  - HHS – 45 CFR 46 (apply to federally-funded research)
  - Academic institutions and most hospitals follow both sets of regulations
  - Sponsors, CROs and private research sites follow FDA regulations
  - Institutionally-based IRBs have to follow both sets of regulations
  - Independent IRBs follow FDA regulations; some chose to follow both sets of regulations

# IRBs are regulated bodies

- An IRB is any board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of, biomedical research involving human subjects. The primary purpose of such review is to assure the protection of the rights and welfare of the human subjects.
  - Must have at least five members of diverse background
  - One member who is not affiliated with the institution and has no family member who is affiliated with the institution, one member who is a non-scientist and one member who is a scientist.
  - A majority of members and the member whose primary concerns are not science must be present to approve research or take other actions.

# Types of IRBs

- Institutionally-based IRBs
  - Universities
  - Hospitals
  - Research institutions
  - Government

Most of these IRBs are part of a nonprofit institution

- Independent IRBs
  - These are for profit, stand alone IRBs
- Central IRBs – Term used to describe an IRB that was developed specifically to review for multiple institutions, such as NCI Central IRB
- Single IRB – Term used to describe an IRB that is designated to review a multi-site protocol. This term is used in revised HHS regulations that are scheduled to go into effect in 2018 if released by the current administration.

# Significant difference and effect on clinical trials

- FDA regulations state that only one IRB is required to review and approve a study.
- HHS regulations requires each institution to have its IRB review a research study or make written arrangements for an external IRB to review a research study on its behalf. This requirement is what has led to “IRB burden” in multi-site research.

# Role of IRB

- The purpose of IRB review is to ensure, both prior to the start of the study/trial and by periodic review, that study is ethically justifiable. This means that the study is designed to protect the rights and welfare of the human subjects.
  - The federal regulations stipulate criteria that the IRB must determine are met in order to approve a study.
  - These criteria are based on the ethical principles that:
    - Individuals should be informed about the methods of the study, risks and potential benefits, and then make an independent decision about participating (Respect for Person)
    - Investigators should do no harm – potential benefits should be reasonable in relation to the risks (Beneficence)
    - No one segment of the population should share the burden of research without also sharing in the benefits (Justice)

# IRB Criteria to Approve Research

- (1) Risks to subjects are minimized: (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.
- (2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies that subjects would receive even if not participating in the research).
- (3) Selection of subjects is equitable.
- (4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative.
- (5) Informed consent will be appropriately documented.
- (6) Where appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.
- (7) Where appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.
- (b) When some or all of the subjects, such as children, prisoners, pregnant women, handicapped, or mentally disabled persons, or economically or educationally disadvantaged persons, are likely to be vulnerable to coercion or undue influence additional safeguards have been included in the study to protect the rights and welfare of these subjects.
- (c) In order to approve research in which some or all of the subjects are children, an IRB must determine that all research is in compliance with part 50, subpart D.



# Research involving individuals who have not reached the age of majority in their state

- Children are defined by state law, usually 18 years old
- Subpart D provides extra protections for children based on the level of risk associated with the research
  - Children give assent
  - Parents give permission
  - Some studies are not permitted

## Studies not involving greater than minimal risk (50.51)

If the IRB finds that:

**(a)** No greater than minimal risk to children is presented; and

**(b)** Adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians.

Studies involving greater than minimal risk and prospect of direct benefit for the individual subject (50.52)

If the IRB finds that:

- (a)** The risk is justified by the anticipated benefit to the subjects;
- (b)** The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and
- (c)** Adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians.

Studies involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subjects' disorder or condition (50.53)

If the IRB finds that:

- (a) The risk represents a minor increase over minimal risk;
- (b) The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;
- (c) The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition that is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and
- (d) Adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians.

.

Clinical investigations not otherwise approvable that present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. (50.54)

These require IRB approval and approval by FDA.

## 50.55 Assent and permission

### Assent of children is required

- (a) In addition to the determinations required under other applicable sections of this subpart D, the IRB must determine that adequate provisions are made for soliciting the assent of the children when in the judgment of the IRB the children are capable of providing assent.
- (b) In determining whether children are capable of providing assent, the IRB must take into account the ages, maturity, and psychological state of the children involved. This judgment may be made for all children to be involved in clinical investigations under a particular protocol, or for each child, as the IRB deems appropriate.

# Assent of children is not a necessary condition for proceeding with the clinical investigation

If the IRB determines:

- (1) That the capability of some or all of the children is so limited that they cannot reasonably be consulted, or
- (2) That the intervention or procedure involved in the clinical investigation holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the clinical investigation.

# Permission of parents

(1) Where parental permission is to be obtained, the IRB may find that the permission of one parent is sufficient for clinical investigations to be conducted under 50.51 or 50.52.

(2) Where clinical investigations are covered by 50.53 or 50.54 and permission is to be obtained from parents, both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.



# Other aspects about assent and permission

- Permission of parents must be documented
- Assent of children is not required to be documented
- The requirement for assent of children or permission of parents may be waived

# What IRBs consider in pediatric research

- Defining the age of majority
- Determining when to waive parental permission
- Taking the psychological development (capacity to understand) into account when obtaining assent – age of 7
- Whether there can be any payment
- How to handle a child's refusal to participate
- How to handle conflict of interest between parents and the child
- Phase 1 trials
- Control group – how to evaluate according to risks and potential benefits

# What is Expanded Access?

- Use of an investigational drug or biologic, outside of a clinical trial, **to treat a patient** with a serious disease or condition who does not have comparable or satisfactory alternative therapies to treat the disease or condition.
  - Intent is clearly **treatment**
- Contrast with investigational drug in a **clinical trial** where the primary intent is **research**
  - systematic collection of data with the intent to analyze it to learn about the drug

# Why Expanded Access?

- Not all patients can wait for approved drugs
  - No effective therapy for condition
  - Exhausted approved options
  - Intolerant of approved products
  - Ineligible or otherwise unable to participate in trials

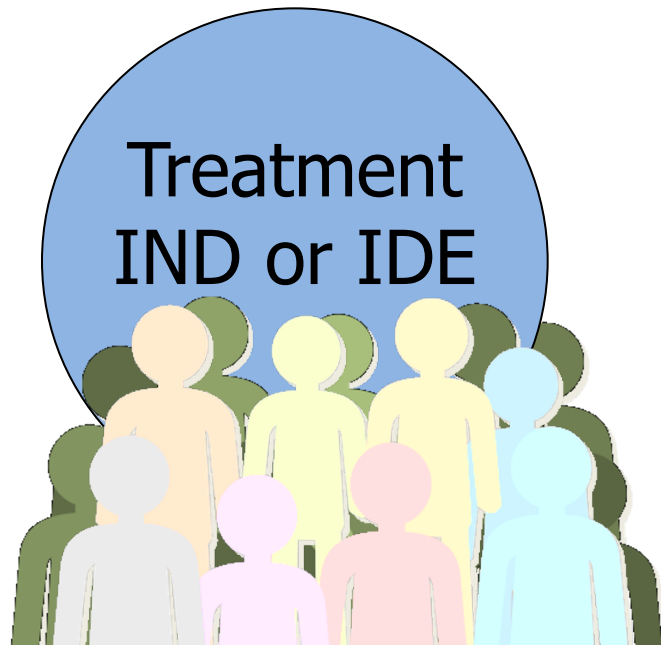
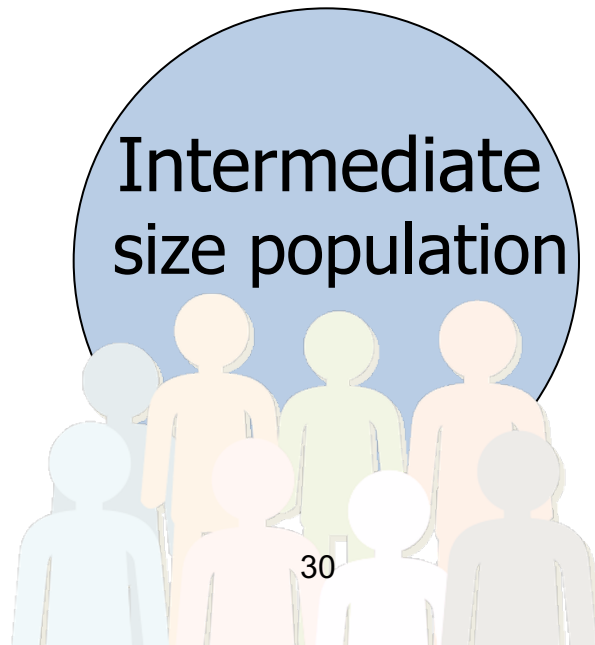
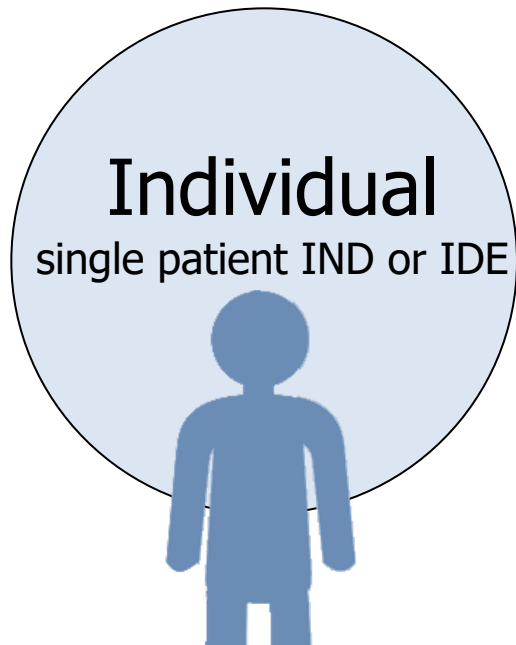
# Expanded Access Program

- FDA approves treatment uses under its expanded access regulations when:
  - The patient and a licensed physician are both willing to participate;
  - The patient's physician determines that there is no comparable or satisfactory therapy available to diagnose, monitor, or treat the patient's disease or condition;
  - That the risk to the patient from the investigational product is not greater than the probable risk from the disease or condition;
  - FDA determines that there is sufficient evidence of the safety and effectiveness of the investigational product to support its use in the particular circumstance;
  - FDA determines that providing the investigational product will not interfere with the initiation, conduct, or completion of clinical investigations to support marketing approval;
  - The sponsor submits a clinical protocol (a document that describes the treatment plan for the patient) that is consistent with FDA's statute and applicable regulations for investigational new drugs applications (INDs) or investigational device exemptions (IDEs), describing the use of the investigational product; and
  - The patient is unable to obtain the investigational drug under another IND or to participate in a clinical trial.
- Note: regulations differs for expanded access uses for investigational medical devices and investigational new drugs and biologics.

# Two Categories of Access Based on Urgency

- Emergency
- Non-emergency

# Three Tiers of Access Based on Size of Group



# Three Tiers of Access Based on Knowledge of Safety and Intent to Market

Limited safety data

Basic safety data exist

Multiple single patients

Not intended to seek marketing approval

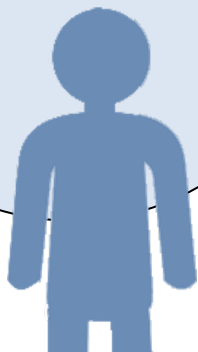
Safety and efficacy data exist

Multiple patients

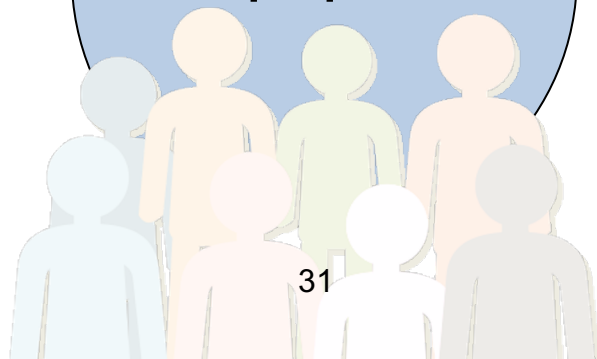
Intended for marketing

**Individual**

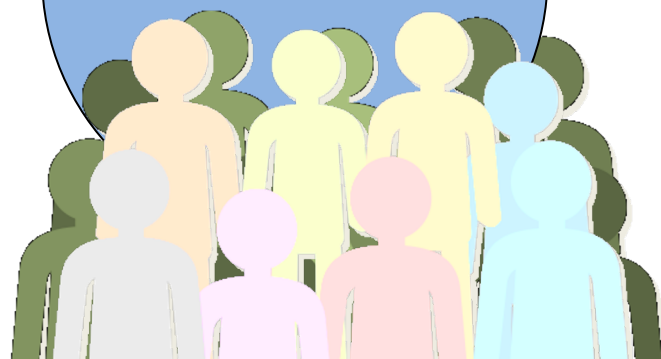
single patient IND or IDE



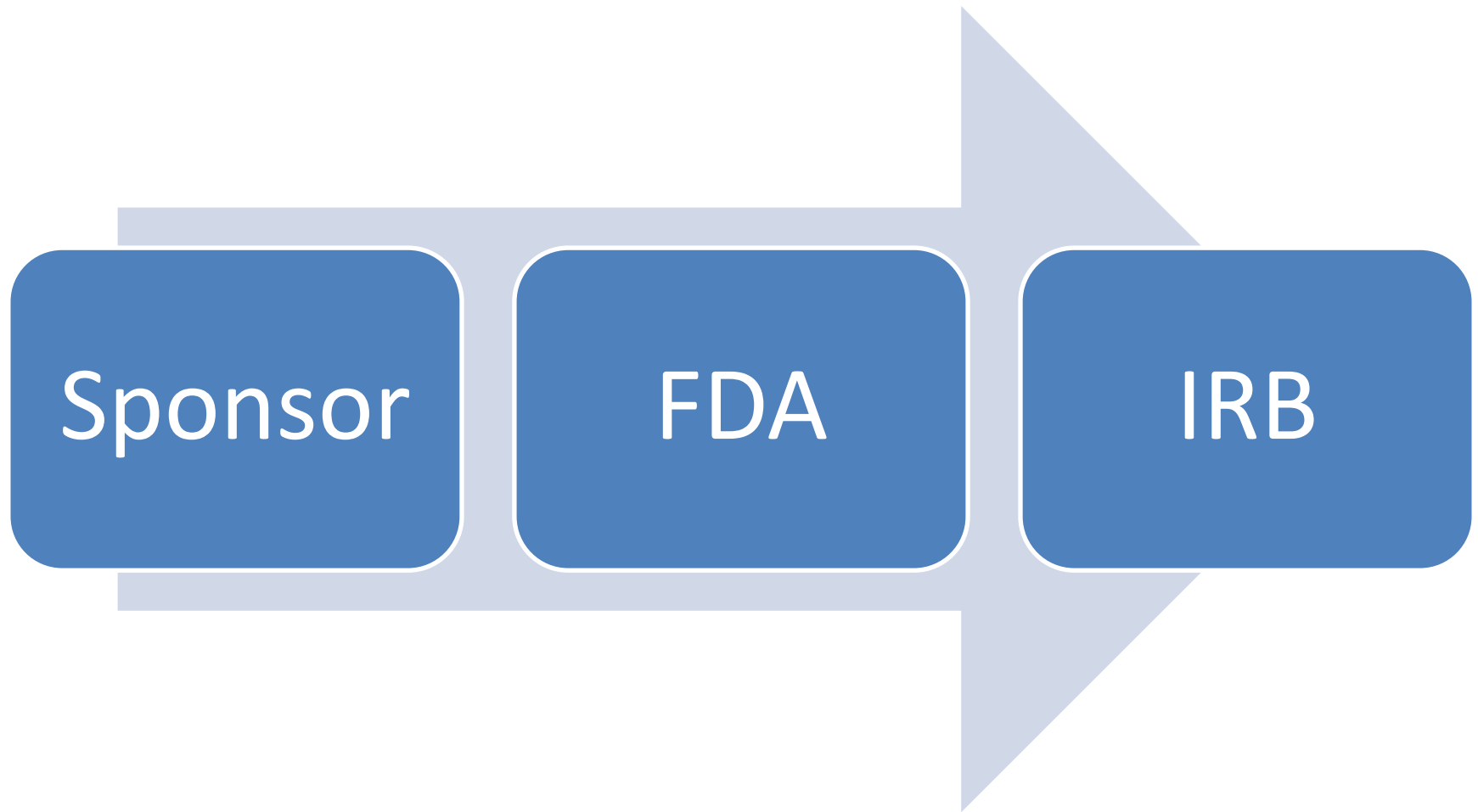
**Intermediate size population**



**Treatment IND or IDE**



# Three step approval process for expanded access uses





# IRB requirements are different depending upon the type of expanded access use and investigational product

- Regulatory requirements for IRBs in reviewing these requests are different for drugs and devices
  - Single patient
    - For devices: IRB chair or designee reviews and concurs with the request
    - For drugs: Convened IRB reviews and approval the request according to the regulatory criteria
  - Intermediate size or wide treatment uses
    - For devices or drugs: the convened IRB reviews and approve a protocol according to the regulatory criteria

# What can IRBs do to help streamline the process of review

- Awareness about request
- Application and submission
- Quick turn-around for review
- Assist IRB members in interpreting review criteria
- Monitoring/tracking the treatment use

# IRB application and submission

- FDA and WCG Foundation encourage IRBs to streamline application:
  - FDA Form 3926
  - Investigator Brochure or another source of information to determine potential risks and benefits
  - Draft consent document
  - Confidentiality and privacy – how to handle

# Quick turn-around time

- Encourage physician to contact IRB when application is submitted.
- Request that the expanded access request is reviewed at the next convened IRB meeting.  
(Note: Non-emergency expanded access requests involving INDs must be reviewed by a convened IRB; an expedited review procedure is not permitted)

# Summary

- Drug approval process is complex and regulated with requirements that sometimes conflict
- IRBs are mandated by regulation, operate in a regulated environment
- IRB criteria for approval of research are broad, which is both an advantage and disadvantage
- Federal regulations are based on a strong protectionist bias toward pediatric research

Qs & As