SPONSOR-INVESTIGATOR TRAINING: INDIVIDUAL PATIENT IND

IND/IDE Support Program

June 8, 2023

Children's Hospital of Philadelphia®

OVERVIEW

- Introduction to the Individual Patient Investigational New Drug (sIND) Application
- Criteria for Individual Patient IND Use
- Key Steps of the Individual Patient IND Application
- Details of the FDA IND Application Process
- FDA Review and Approval: Process Steps and Reporting
- Withdrawal (Closure) of the Individual Patient IND
- References

INTRODUCTION TO THE sIND

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TYPES OF FDA-REGULATED CLINICAL TRIALS

- **Phase 1-4 standard FDA IND clinical trials**
  - Includes Pilot, First-in-human, First-in-children

- **Expanded access**
  - Emergency use of a drug, biologic, or device to treat a patient
  - Wide-spread use
  - Intermediate-size patient population
  - **Individual patient**

TWO TYPES OF INDIVIDUAL PATIENT INDs AT CHOP

- The majority of sponsor-investigator IND studies at CHOP currently are:
  - Single Patient IND (sIND)
  - Emergency Single Patient IND (eIND)
- The treatment provided to patients can be either drugs or biologics
- The drug/biologic used may be investigational OR lawfully marketed

AN sIND MIGHT BE NEEDED IF…

- The patient's disease is not listed in the FDA label for that indication
- The drug is not approved for marketing in the US
  - For example, the drug is only approved in another country, is in development in the US, or is a supplement or food not approved for marketing as a drug
- The drug is approved for a use other than the proposed use
  - If the investigation involves a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drug product (21 CFR 312.2 (b) (1) (iii))

CRITERIA FOR A SINGLE PATIENT IND

- The patient has a serious or immediately life-threatening disease or condition
- There is no comparable or satisfactory alternative therapy to diagnose, monitor or treat the disease or condition
- The patient does not meet eligibility criteria for an existing clinical trial
- The potential patient benefit justifies the potential risks of the treatment use, and the risks the patient might experience are not unreasonable in the context of the disease or condition
- The sIND will not interfere with the initiation, conduct or completion of clinical investigations that could support marketing approval or compromise development of the expanded access use

GOALS OF A SINGLE PATIENT IND

- Provide investigational drug or biologic to a single patient to **treat** their disease.
- Assess clinical benefit and toxicity of the investigational product in the patient

OBTAIN APPROVAL FROM DRUG MANUFACTURER TO PROVIDE PRODUCT

- Contact the manufacturer to request approval of drug for your patient
  - Describe the patient's clinical condition and rationale for drug use
  - The manufacturer's approval could be a formal letter or an email and is called a "Letter of Authorization" or LOA
  - Also request:
    - An Investigator's Brochure, which contains drug risk information, which will be incorporated into the ICF
    - A Pharmacy Manual, if applicable, which contains storage information and the method of reconstitution
    - Safety Data Sheet SDS for unapproved drugs

COMPLETE FDA SUBMISSION

Documents to Include
Cover Letter
FDA Form 3926
Treatment Plan
Letter of Authorization
Informed Consent form*
Investigator's Brochure
Sponsor's CV or Biosketch
2-3 Key Publications**

*Usually not required but may be requested by FDA reviewer
**Please include, especially for novel treatments

CHOP IRB SUBMISSION

- Complete the IRB application for an individual patient in eIRB
- Upload the Letter of Authorization*
- Upload the Investigator's Brochure (IB), if available
- Upload the completed FDA Form 3926
- Upload the Treatment Plan
- Upload the Informed Consent Form for this single patient
- Submit the eIRB application for division head approval

*Email confirmation from drug manufacturer is generally acceptable

CONTACT IND/IDE SUPPORT FOR ASSISTANCE

- Contact IND/IDE Support at INDIDE@CHOP.edu, if help is needed
- IND/IDE Support will help your study team assemble, review and submit your submission to the FDA
- Per CHOP Policy, all FDA correspondence is required to be shared with IND/IDE Support
- Contacts at IND/IDE Support:
  - INDIDE@chop.edu
  - wentworthm@chop.edu Mark Wentworth
  - jonesa40@chop.edu Anja Jones
  - podsakoff@chop.edu Greg Podsakoff

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INFORM THE INVESTIGATIONAL DRUG SERVICES

- Inform the Investigational Drug Services (IDS) about your pending single patient IND at InvestigationalPharmacy@chop.edu
  - Please include Patient name, MRN, treatment summary, IRB #, drug name and manufacturer, and estimated start date of dosing
- Provide IDS with the Investigator's Brochure, Pharmacy Manual (if applicable), and Safety Data Sheet for unapproved drugs
- For unapproved drugs, when the product arrives the IDS will collect and keep a Certificate of Analysis which certifies that drug release criteria are met
- Ask the IDS for best practices regarding the monitoring of drug compliance

INFORM THE OFFICE OF RESEARCH COMPLIANCE

- Inform the Office of Research Compliance (ORC) about your pending single subject IND at ORC@chop.edu

- ORC may schedule a quality assurance review of the single subject IND at any time while the IND is active

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ASK CONTRACTS ABOUT THE NEED FOR A sIND AGREEMENT

- Generally, a contractual agreement is not required to conduct a single patient IND at CHOP
- However, some drug manufacturers may require a contractual agreement before drug is shipped
- If the manufacturer requests a contract, contact Contracts (researchcontracts@chop.edu) to help execute the contract before drug delivery
  - Review executed contract for any reporting requirements (e.g. AEs of special interest)

ELEMENTS OF THE FDA sIND APPLICATION

COVER LETTER

- IND/IDE Support has developed a draft cover letter, with template language for use
- In the cover letter, you may want to include the planned treatment date (especially if the date is in less than 30 days)

FDA FORM 3926: OVERVIEW

- The FDA Form 3926 is a streamlined single patient IND application (replacing FDA Forms 1571 and 1572), available to download from the FDA website
- The IND/IDE Support Office recommends completing the FDA Form 3926 in summary manner and attaching a separate, more complete Treatment Plan to the form*
- Information requested in the FDA Form 3926 should also be included in the completed Treatment Plan

*Some drug manufacturers request their own sIND template or Treatment Plan be completed – If so, follow the manufacturer's template

FDA FORM 3926

Sections of the Form for an Initial Submission:

1-3) Patient Initials, Date of Submission, Type of Submission, Investigational Drug Name.

As indicated in Box 3a, for an initial submission, complete Fields 4-8, 10,11. Do not complete other fields.

4) Clinical Information: Include indication, patient description, clinical course, and rationale for the use of the drug for this patient - usually in 1-2 paragraphs

5) Treatment Information: Provide a description of the Investigational drug, usually in approximately 1-2 sentences

FDA FORM 3926

6. Letter of Authorization (LOA), if applicable *(generally obtained from the manufacturer of the drug)*

☐ I have attached the LOA. *(Attach the LOA; if electronic, use normal PDF functions for file attachments.)*

Note: If there is no LOA, consult the Form Instructions.

7. Physician's Qualification Statement *(Including medical school attended, year of graduation, medical specialty, state medical license number, current employment, and job title. Alternatively, attach the first few pages of physician's curriculum vitae (CV), provided they contain this information. If attaching the CV electronically, use normal PDF functions for file attachments.)*

8. Physician Name, Address, and Contact Information

Physician Name *(Sponsor)*		Email Address of Physician
Address 1 *(Street address, No P.O. boxes)*		
Address 2 *(Apartment, suite, unit, building, floor, etc.)*		Telephone Number of Physician
City	State	Facsimile (FAX) Number of Physician
ZIP Code		Physician's IND number, if known

9. Contents of Submission

This submission contains the following materials, which are attached to this form (select all that apply). If none of the following apply to the follow-up communications, use Form FDA 1571 for your submission.

☐ Initial Written IND Safety Report
☐ Follow-up to a Written IND Safety Report
☐ Annual Report
☐ Summary of Expanded Access Use (treatment completed)
☐ Change in Treatment Plan
☐ General Correspondence
☐ Response to FDA Request for Information
☐ Response to Clinical Hold

Section 6: Check box to indicate you are attaching a Letter of Authorization

Section 7: Select "Please see attached" to indicate you are including the Sponsor's CV in the FDA submission

Section 8: Provide the Sponsor's contact information as indicated

FDA FORM 3926: EXPEDITING IRB REVIEW

- In Section 10, check both boxes ‘a’ and ‘b’

- This allows the sIND to be reviewed by an IRB Chair instead of by the full Board, which **expedites** the review.

10.a. Request for Authorization to Use Form FDA 3926

☒ I request authorization to submit this Form FDA 3926 to comply with FDA’s requirements for an individual patient expanded access IND.

10.b. Request for Authorization to Use Alternative IRB Review Procedures

☒ I request authorization to obtain concurrence by the Institutional Review Board (IRB) chairperson or by a designated IRB member, before the treatment use begins, in order to comply with FDA's requirements for IRB review and approval. This concurrence would be in lieu of review and approval at a convened IRB meeting at which a majority of the members are present.

FDA FORM 3926

- Section 11 includes the Certification Statement that Sponsors must agree to by signing the document
- The signature may be electronic or wet-ink

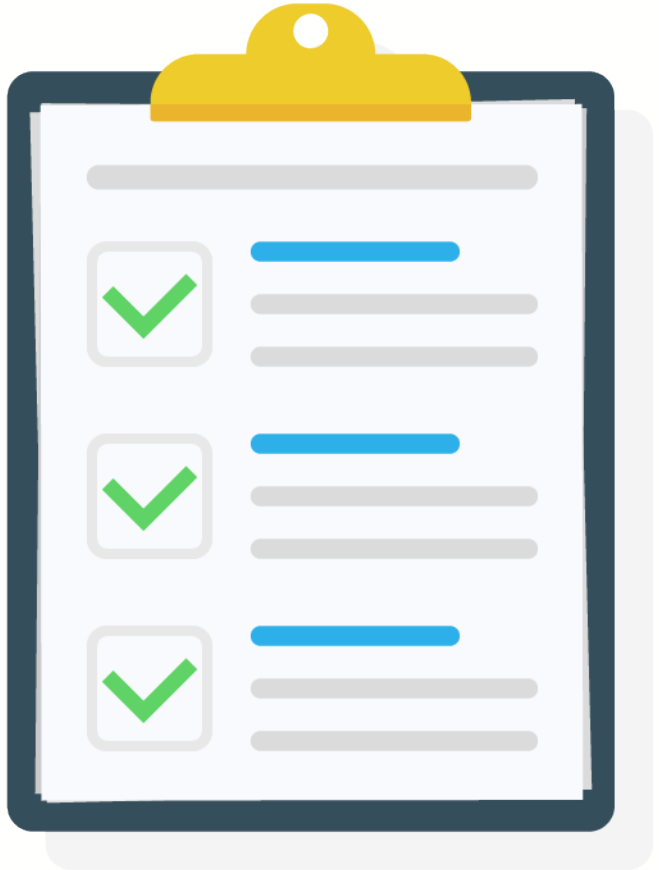
11. Certification Statement: I will not begin treatment until 30 days after FDA's receipt of a completed application and all required materials unless I receive earlier notification from FDA that treatment may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I also certify that I will obtain informed consent, and that an Institutional Review Board (IRB) will be responsible for initial and continuing review and approval of this treatment use, consistent with applicable FDA requirements. I understand that in the case of an emergency request, treatment may begin without prior IRB approval, provided the IRB is notified of the emergency treatment within 5 working days of treatment. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

WARNING: A willfully false statement is a criminal offense (U.S.C. Title 18, Sec. 1001).

Signature of Physician	**Date**

TREATMENT PLAN

- As you develop your treatment plan, keep in mind that a single patient IND is considered treatment of a patient using an investigational drug/biologic, and should follow clinical care practices as much as feasible
- A single patient Treatment Plan template is available to download from the CHOP IRB protocol templates webpage



COMPLETING THE TREATMENT PLAN

Elements to Include	What Information is provided
Dosing	Provide the plans for duration of use of drug, route of administration, specifics of daily or weekly or monthly dosing; drug handling/accountability (diary or pill counts)
Dose modification	Provide dosing contingencies if the drug is ineffective at a given dose, or if there is toxicity at a certain dose. Also specify if/when dose modifications should occur based on changes in weight/BSA
Monitoring	Document how the sponsor, investigator or study coordinator will monitor the study on a regular basis, as documented by filing a brief report to the patient's study documents summarizing that compliance, completeness and accurateness of records are in order Include ORC monitoring frequency

COMPLETING THE TREATMENT PLAN, CONT'D

Elements to Include	What information is provided?
Adverse event reporting: Definition of severity grades	Grade 1 – Abnormality, no clinical action. Reported in annual report Grade 2 – Abnormality, clinically actionable. Reported in annual report Grade 3 – Event that results in hospitalization, or prolongation of hospitalization (not an elective hospitalization) Grade 4 – Event that is life-threatening, and includes death. Adverse event reporting section should also include how and what will be reported to the IRB and FDA, as well as drug manufacturer (if applicable)
Adverse event reporting: Timing	Grade 1 – Reported in FDA annual report Grade 2 – Reported in FDA annual report Grade 3 – Expedited reporting (within 7 days, using MedWatch Form 3500A (downloadable) Grade 4 – Expedited reporting (within 3 days, using MedWatch Form 3500A (downloadable)

INFORMED CONSENT

- A draft single patient Informed Consent Form is usually not required for the FDA submission, but is a good to have on hand in case it is requested by the FDA

- As part of the IRB submission, you will develop an Informed Consent Form

- There is a template single patient Informed Consent Form on the IRB website: https://irb.research.chop.edu/consent-templates

FDA REVIEW AND APPROVAL: PROCESS AND REPORTING

FDA REVIEW: RESPONSE TIMELINES

- Single patient INDs are under review for 30 days upon receipt of the submission
- During this time, the agency may reach out with additional questions or clarifications. The sIND Sponsor should be available to answer in a timely manner
- Single patient INDs may be permitted to proceed prior to the 30-day review period, but ONLY if written approval is granted by the FDA

AFTER sIND APPROVAL

- Conduct the sIND according to the Treatment Plan
- If there are changes to the sIND (e.g. treatment plan, drug supplier, Sponsor), submit an amendment to both the IRB and the FDA. Training supplement contains detailed instructions as to what documents are to be submitted to the FDA
- SAE's that meet reporting criteria need to be submitted to the IRB and FDA*
- File Annual Reports** annually, within +/- 60 days of the anniversary date (the date that the sIND went into effect)
- Once drug treatment is complete, withdraw the sIND**
  - Also inform IDS and confirm final drug disposition

*SAE reporting criteria should be included in the Treatment Plan
**Email IND/IDE Support to request "Annual Report" and "Withdrawal of IND" templates

REFERENCES

- CFR - Code of Federal Regulations: 21 CFR 312
- https://www.fda.gov/drugs/investigational-new-drug-ind-application/physicians-how-request-single-patient-expanded-access-compassionate-use

Gregory M Podsakoff, M.D.

Digitally signed by Gregory M Podsakoff, M.D.
DN: cn=Gregory M Podsakoff, M.D., o=Children's Hospital of Philadelphia, ou=IND-IDE Support Program, CRSO, email=podsakoff@chop.edu, c=US
Date: 2023.06.21 15:30:30 -04'00'

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