IMPAACT Protocol Chair Roles and Responsibilities: Pre-Implementation

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19 September 2022

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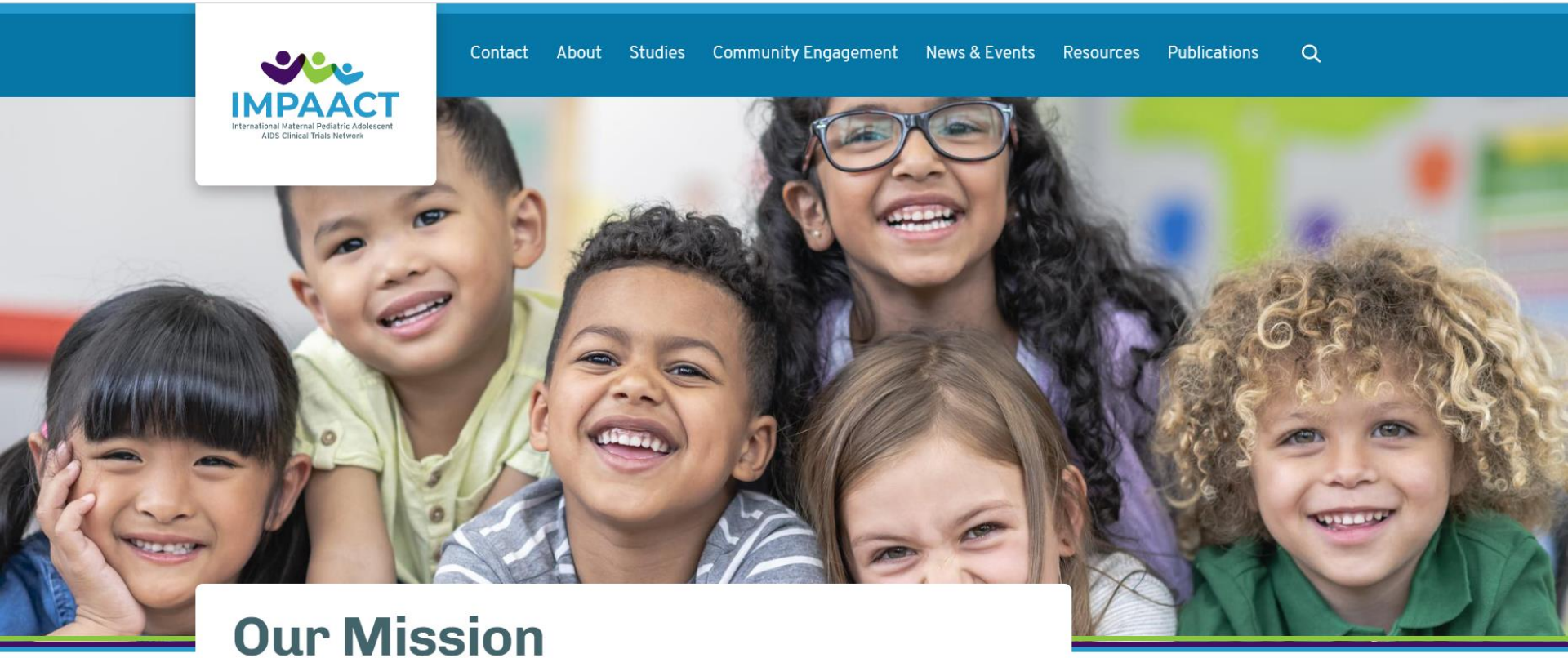
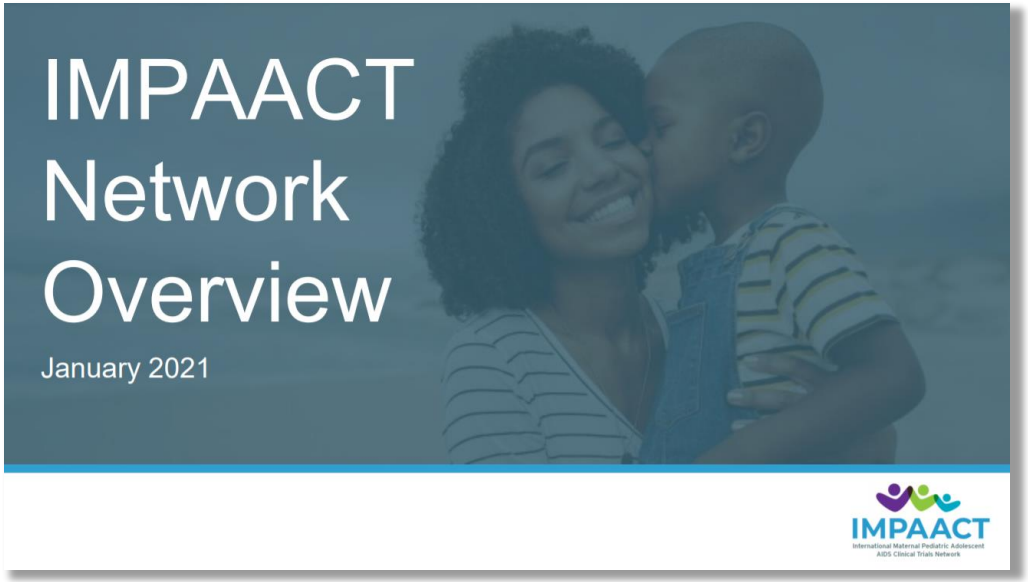
Please Visit Our Website



To learn more about the overall Network, please review the Overview presentation



https://www.impaactnetwork.org/sites/default/files/2021-03/IMPAACT%20Overview_JAN2021-PDF.pdf

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Refer to the IMPAACT Protocol Chair Roles and Reponsibilities: Overview and Activities during Protocol Development presentation for additional information

https://www.impaactnetwork.org/resources/manual-procedures

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Study-Specific Pre-Implementation Activities

IMPAACT Network Manual of Procedures,
Section 11, Study-Specific Pre-Implementation Activities

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Pre-Implementation Responsibilities

From initiation of protocol development through first enrollment

Work with the CRM to complete the site selection process
(MOP Section 10)

Work with the CRM to develop the study budget
(MOP Section 11.1.11)
budget negotiations with study partners are handled at the Network level

Lead protocol development process with the CRM
(MOP Section 9)

Work with the CRM to develop and carry out study-specific training plans
(MOP Section 16)

Ensure timely development and sign-off of study implementation plans and materials
(MOP Section 11)

Open to Accrual Requirements

- Study-specific preparatory steps must be completed before an IMPAACT study can be designated as open to accrual
- “Open to accrual” and other Division of AIDS (DAIDS) study statuses are defined at https://rsc.niaid.nih.gov/sites/default/files/StudyStatusProtocolMgmtOct2015.pdf

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Open to Accrual Requirements

- Protocol Chair and CRM work closely with other team members to identify and track all requirements that must be met to open each study to accrual
- Some requirements apply to all studies, while others may be study-specific (see IMPAACT Network MOP Section 11.1)
- The CRM develops and maintains a checklist to track the status of open to accrual requirements

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IMPAACT 2034: Phase I Study of the Pharmacokinetics, Safety, and Acceptability of a Single Dose of Pretomanid Added to an Optimized Background Regimen in Children with Rifampicin-Resistant Tuberculosis
Protocol Version 1.0 Open to Accrual Checklist

Open to Accrual Requirement	Responsible Members	Completion Date	Comments
Protocol Version 1.0 Distributed to Sites	CRMs	04 AUG 2022	
Clinical Trials Agreement Finalized	DAIDS/TBA	27 JAN 2022	
ClinicalTrials.gov Registration	DAIDS		
Receipt of "Safe to Proceed" Notice from DAIDS	DAIDS	06 SEP 2022	
Study Drug Available at CRPMC	PAB		
Laboratory Processing Chart (LPC) Finalized and Distributed to Sites	LTs with LC		
Pharmacokinetic (PK) testing lab readiness	LC		
Preloads finalized and available for site use in LDMS	LDM		
Manual of Procedures (MOP) Finalized and Distributed to Sites	CRMs		
IMPAACT Data Management Center (DMC) confirms DMC readiness for the study • Electronic case report forms (eCRFs) finalized and available for site use in Medidata Rave • Enrollment screens available in Study Enrollment System (SES)	PDMs		
Study Progress, Data, and Safety Monitoring Plan (SPDSMP) finalized	Statisticians		
Pharmacology Data Management Plan (PK DMP) finalized	LDMs		
Primary PK Statistical Analysis Plan (SAP) finalized	Pharmaco-metricians		
Primary SAP finalized	Statisticians		
Study budget finalized and approved by IMPAACT leadership	CRMs	22 JUN 2022	
Fully executed agreement between IMPAACT Finance Group and IQVIA for centralized ECG	JHU Finance Group		
DAIDS study trial master file (TMF) has been initiated	DAIDS	27 JUN 2022	
Open to Accrual Message Distributed to Protocol Team and Sites	CRMs		

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Open to Accrual: Protocol Chair Roles and Responsibilities

- The Protocol Chair works with the CRM to ensure the overall timely development and sign-off of study implementation plans and materials
- Protocol team members take the lead on preparing specific materials, with Chair input and sign-off obtained where applicable, as outlined below

Clinical Trials Agreement (CTA)

Background/ Development

- A CTA is typically negotiated between a collaborating pharmaceutical company and DAIDS to document responsibilities and rights of each party

Team Review

- DAIDS CTA Team may seek input and review of CTAs by the protocol chair, MOs, and SDMC Principal Investigator, who consults with SDMC representatives on protocol team, as needed, during negotiations

Timing

- Typically initiated when protocol is submitted for DAIDS P/CSRC review

Responding to US Food and Drug Administration (FDA) Comments

Background/ Development	Team Review	Timing
• If sufficient safety concerns are identified during the FDA review of the protocol, a Clinical Hold may be issued, and the study may not open to accrual until the issues are resolved	• Protocol team (led by CRMs and chair) coordinates with DAIDS MO and DAIDS RAB to respond to FDA	• Team must respond to comments within the timeframe specified by the FDA (timeframes might be very short!)

Laboratory Processing Chart (LPC)

Background/ Development

- An LPC is developed for most IMPAACT studies as a detailed laboratory-related companion to the protocol
- The laboratory technologist (LT) develops the LPC with the protocol IMPAACT Laboratory Center (LC) representative; the protocol laboratory data manager (LDM) and CRM also contribute to the LPC development

Team Review

- The full protocol team is responsible for reviewing the draft LPC, with sign-off required from protocol chair(s), LC representative, LT, LDM, and CRM

Timing

- LPC development typically begins when the protocol is in the final stages of development

Participant Enrollment Materials

Background/ Development

- Protocol data manager (PDM) prepares draft eligibility checklist corresponding to study-specific inclusion and exclusion criteria

Team Review

- Protocol team reviews draft eligibility checklist, with sign-off required from protocol chair(s), DAIDS MO, and protocol statistician(s)

Timing

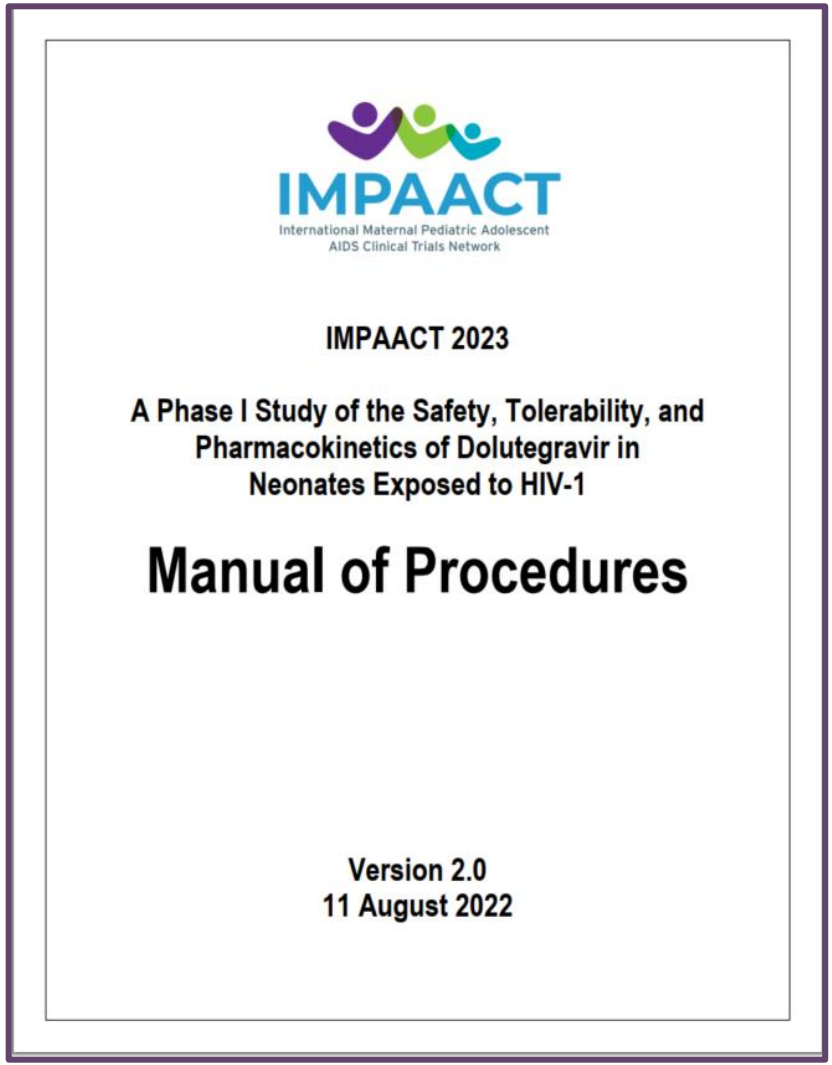
- Eligibility checklist development typically begins when the protocol is in the final stages of development

Data Collection Materials

Background/ Development	Team Review	Timing
• The PDM develops draft data collection instruments and associated materials	• Data collection instruments are reviewed by the protocol team, DMC, SDAC, and the IMPAACT eCRF Committee prior to final team review and sign-off by protocol chair(s), DAIDS MO, and statistician(s)	• Development of data collection materials begins following approval of the protocol by DAIDS P/CSRC

Study-Specific Manual of Procedures (MOP)

- A study-specific MOP serves as an operational resource for implementation of IMPAACT studies
- The purpose of a study-specific MOP is to supplement the protocol with further information to optimize adherence to study protocols and standardization of study procedures across sites



Study-Specific Manual of Procedures (MOP)

Background/ Development

- The CRM coordinates the development and review of all MOP sections with the protocol chair and other protocol team members
- Some team members may be assigned primary authorship responsibilities, as outlined in IMPAACT Network MOP Table 11-1

Team Review

- The full protocol team reviews draft sections of the MOP, with sign-off on all sections required from the protocol chair, CRM, and DAIDS MO

Timing

- Study-specific MOP development typically begins when the protocol is in the final stages of development

Table 11-1. Protocol Team Member Study-Specific MOP Responsibilities and Requirements

Protocol Team Member	Responsibilities and Requirements
Protocol Chair and DAIDS MO	Responsible for review and sign-off of all sections
Protocol Data Manager	Responsible for authorship, review, and sign-off of sections related to data collection and management
Protocol Lab Specialist and Laboratory Technologist	Responsible for authorship, review, and sign-off of sections related to specimen collection, processing, testing, shipping, and other related sections
Protocol Investigators	Responsible for input and review of sections related to clinical or other specialized procedures and safety reporting
Protocol Pharmacist	Responsible for authorship, review, and sign-off of sections related to study product and study product management
Protocol Pharmacologist	Responsible for authorship, review, and sign-off of sections related to PK procedures and considerations for study implementation, if applicable
CRM	Responsible for authorship and review of sections related study overview, documentation requirements, accrual and retention, informed consent, study procedures, safety and clinical procedures, counseling, and any other sections related to study-specific requirements; responsible for review and sign-off of all sections
Protocol Statistician	Responsible for review of relevant sections

Study Progress, Data, and Safety Monitoring Plan (SPDSMP)

Background/ Development

- Protocol statisticians and PDMs develop an SPDSMP that details:
  - The accumulating study data to be monitored
  - The type, frequency, and content of monitoring reports that will be generated
  - Responsibilities for generating, receiving, and reviewing database monitoring reports

Team Review

- Input from all team members, and the SMC or DSMB, is incorporated into the final SPDSMP, with sign-off obtained from the SDMC protocol team members and the DAIDS MO

Timing

- The near-final SPDSMP is reviewed during the initial SMC/DSMB review; thereafter, it is finalized approximately concurrent with the study protocol and before the study is opened to accrual

Pharmacology (PK) Data Management Plan

Background/ Development	Team Review	Timing
• For studies that include PK evaluations, the LDMs (with the protocol pharmacologist and PDMs) develop a PK Data Management Plan	• Input from all team members is incorporated into the final PK Data Management Plan, with sign-off obtained from the protocol chairs, pharmacologists, statisticians, PDMs, and LDMs	• The near-final PK Data Management Plan is reviewed during the initial SMC/DSMB review; thereafter, it is finalized approximately concurrent with the study protocol and before the study is opened to accrual

Statistical Analysis Plan (SAP)

Background/ Development

- The protocol statisticians draft a primary SAP that details the analyses to be performed to fulfill the study objectives
- When applicable, additional SAPs may be prepared (e.g., for secondary publications); for PK studies, protocol pharmacologist prepares a pharmacology SAP

Team Review

- The protocol team receives a near-final draft of the primary SAP for review and comment, and the final version of the primary SAP is approved by the protocol statisticians

Timing

- Development of the primary SAP typically begins when the protocol is in the final stages of development

Site-Specific Study Activation

- The CRM coordinates the development and review of a study-specific template checklist in close cooperation with the protocol chair and other protocol team members
- Some protocol team members are typically assigned responsibilities for confirming elements of activation for each site, as outlined in the generic, template activation checklist, posted on the IMPAACT website:

https://www.impaactnetwork.org/resources/manual-procedures

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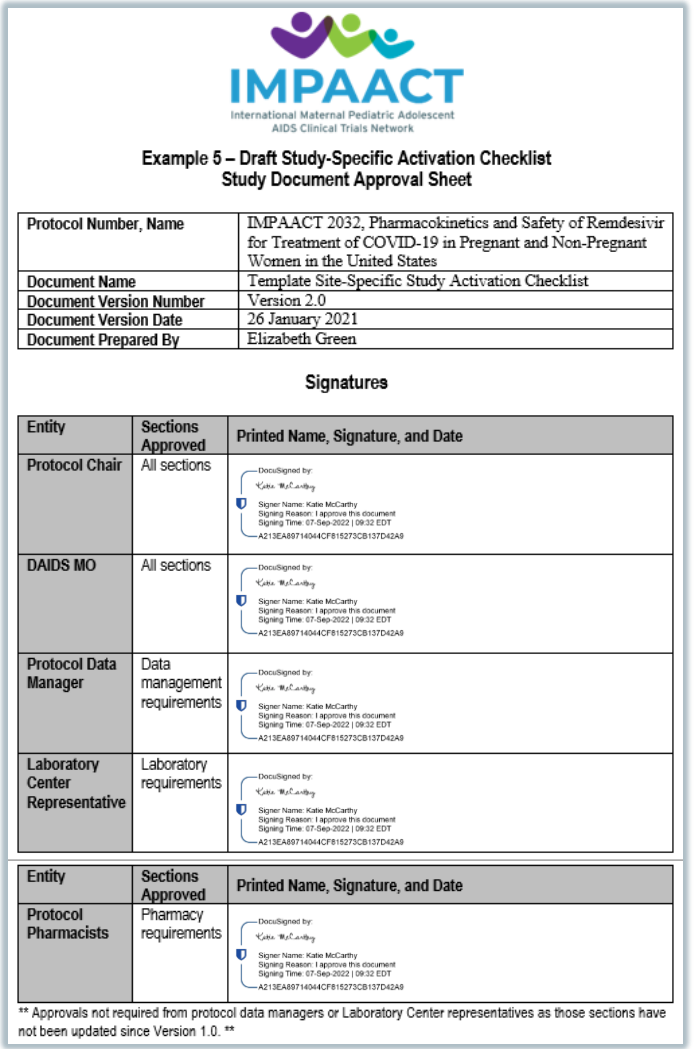
Site-Specific Study Activation

- Sign-off of all sections of the study-specific template checklist is required from the protocol chair and DAIDS MO
- Sign-off on applicable sections is required from the PDM, LC representative, and protocol pharmacist (these representatives also actively participate in the activation process with sites and the CRM)



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Example 5 – Draft Study-Specific Activation Checklist
Study Document Approval Sheet

Protocol Number, Name	IMPAACT 2032, Pharmacokinetics and Safety of Remdesivir for Treatment of COVID-19 in Pregnant and Non-Pregnant Women in the United States
Document Name	Template Site-Specific Study Activation Checklist
Document Version Number	Version 2.0
Document Version Date	26 January 2021
Document Prepared By	Elizabeth Green

Signatures

Entity	Sections Approved	Printed Name, Signature, and Date
Protocol Chair	All sections	DocuSigned by: Katie McCarthy Signer Name: Katie McCarthy Signing Reason: I approve this document Signing Time: 07-Sep-2022 | 09:32 EDT A213EA89714044CF815273CB137D42A9
DAIDS MO	All sections	DocuSigned by: Katie McCarthy Signer Name: Katie McCarthy Signing Reason: I approve this document Signing Time: 07-Sep-2022 | 09:32 EDT A213EA89714044CF815273CB137D42A9
Protocol Data Manager	Data management requirements	DocuSigned by: Katie McCarthy Signer Name: Katie McCarthy Signing Reason: I approve this document Signing Time: 07-Sep-2022 | 09:32 EDT A213EA89714044CF815273CB137D42A9
Laboratory Center Representative	Laboratory requirements	DocuSigned by: Katie McCarthy Signer Name: Katie McCarthy Signing Reason: I approve this document Signing Time: 07-Sep-2022 | 09:32 EDT A213EA89714044CF815273CB137D42A9

Entity	Sections Approved	Printed Name, Signature, and Date
Protocol Pharmacists	Pharmacy requirements	DocuSigned by: Katie McCarthy Signer Name: Katie McCarthy Signing Reason: I approve this document Signing Time: 07-Sep-2022 | 09:32 EDT A213EA89714044CF815273CB137D42A9

** Approvals not required from protocol data managers or Laboratory Center representatives as those sections have not been updated since Version 1.0. **

Laboratory Activation Checklists

- Laboratory-related activation requirements for each study are outlined on a study-specific template laboratory activation checklist for each study
- The study-specific template laboratory activation checklist is developed in parallel with the overall study activation checklist
- Final approval of the study-specific template laboratory activation checklist is provided by the DAIDS Clinical Laboratory Team (DCLOT) to the Laboratory Center

Initial Study Monitoring Committee (SMC) Review

IMPAACT Network Manual of Procedures,
Section 13.5, IMPAACT Study Monitoring Committee Review

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Purpose of SMC

- In support of the management and oversight functions of the MOG, for designated studies, an IMPAACT SMC monitors participant safety and the progress and quality of IMPAACT study conduct
- Based on its reviews, the SMC makes recommendations related to study continuation, including cohort progression and dose selection, when applicable
- Scope of SMC reviews varies across studies, depending on protocol specifications

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SMC Membership, Roles, and Responsibilities

IMPAACT Network MOP Section 13.5.1 and Table 13-1

https://www.impaactnetwork.org/resources/manual-procedures

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Purpose of Initial SMC Review

- Review and discuss near final draft SPDSMP with protocol chair, statistician, CRM, and other team members
- Orient SMC members to the study protocol and agree upon:
  - Key specifications of the SPDSMP
  - Required frequency of SMC reviews for the study
  - Criteria for triggered SMC reviews, if applicable
  - Data to be presented in reports prepared for SMC review

Timing of Initial SMC Review

- Initial review occurs in late stages of protocol development to enable the SPDSMP to be finalized approximately concurrent with the protocol and prior to opening the study to accrual

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Preparation for Initial SMC Review

- Protocol chair works with protocol statistician and other team members as needed to prepare a presentation for the initial review
- Protocol chair presentation (<10 minutes):
  - Briefly review study rationale, objectives, and design
  - Highlight key issues the protocol team would like to emphasize for consideration by the SMC
- Protocol statistician presentation (<15 minutes):
  - Briefly highlight statistical design of study
  - Present key aspects of SPDSMP, including an overview of the types of monitoring data reports to be provided to protocol team and SMC
  - Note any protocol-specified triggers for ad hoc SMC reviews

Study-Specific Training

IMPAACT Network Manual of Procedures,
Sections 11.2.10 and 16.6, Study-Specific Training

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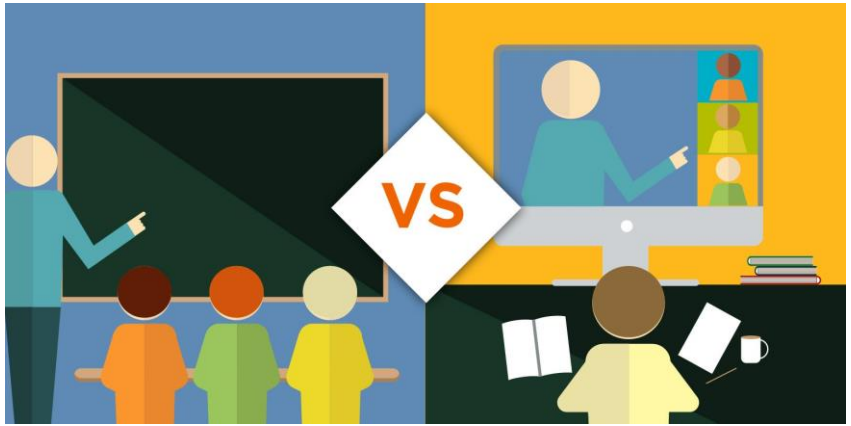
Study-Specific Training

- Site Investigators of Record (IoRs) are responsible for ensuring that site study staff members are adequately trained to perform their delegated study-specific functions
- Protocol teams collaborate with IoRs to fulfill this responsibility by conducting study-specific training



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Study-Specific Training

- Protocol team agrees on a study-specific training plan tailored to needs of the study and the participating sites
- Once a study-specific training plan is finalized, the operational approach is communicated to the study sites, and training timelines and materials are developed. The CRM coordinates with the Protocol Chair, SDMC, and LC to lead these training efforts, with input from protocol pharmacists, and medical officers, as needed

Guidelines for Scheduling IMPAACT Study-Specific Training

To be completed prior to scheduling study-specific training (as applicable to the study; see Section 11 for details related to study-specific pre-implementation activities):
• Completion of US Food and Drug Administration (FDA) 30-day review period/safe to proceed notice • Signed Clinical Trials Agreement(s) (CTA) • Study product(s) available at the DAIDS Clinical Research Product Management Center (CRPMC) • Finalization of the study-specific MOP for use as a reference during training (Note: a draft version may be used for training purposes) • At least one site close to meeting all activation requirements, such that activation and initiation of the study will occur upon (or very soon after) completion of training
Note: Sites that have made significant progress towards meeting study-specific site activation requirements, as outlined in Section 11, will be prioritized when scheduling study-specific training. However, other sites may be invited to participate in training sessions, as determined in the training plan.

Minimum Topics to be Covered for IMPAACT Study-Specific Trainings

- Study Overview including Rationale and Objectives
- Study-Related Communications
- Informed Consent Considerations
- Eligibility Criteria
- Screening and Enrollment Process
- Study Procedures (covering protocol Section 6 and the Schedules of Evaluation)
- Pharmacy and Study Drug Considerations
- Data Management Considerations
- Laboratory Considerations
- Toxicity/Participant Management
- Adverse Event and Expedited Adverse Event Reporting
- If needed, Network structure and procedures overview (including deviation reporting)
- Other study- or site-specific topics may be added

Other IMPAACT Protocol Chairs

Study	Chairs
IMPAACT 2037, Open-Label, Phase I Study of the Safety and Pharmacokinetics of PGT121.414LS alone and in combination with VRC07-523LS in Infants Exposed to HIV-1	Coleen Cunningham, Univ California, Irvine, United States Elizabeth (Betsy) McFarland, Univ Colorado Denver, United States
IMPAACT 2036, Safety & PK of Long-Acting Cabotegravir and Rilpivirine in Children	Mo Archary, UKZN, South Africa Jorge Pinto, UFMG, Brazil
IMPAACT 2035, Safety & Immunogenicity of TB Vaccines	Lisa Cranmer, Emory, United States Cheryl Day, Emory, United States
IMPAACT 2034, PK & Safety of Pretomanid in Children with MDR-TB	Ethel Weld, JHU, United States Tony Garcia-Prats, Univ Wisconsin, United States Pauline Howell, Sizwe Tropical Disease Hospital, South Africa
IMPAACT 2024, Dose-Finding & Safety of Daily Rifapentine with Isoniazid in Children	Nicole Salazar-Austin, JHU, United States Christy Beneri, Stony Brook, United States

Other IMPAACT Protocol Chairs

Study	Chairs
IMPAACT 2039, Phase I/II Study of the Safety, Immunogenicity, Efficacy of HIVconsvX Vaccines in Children Living with HIV	Mark Cotton, FAMCRU/Stellenbosch, South Africa Avy Violari, PHRU Chris Hani Baragwanath, South Africa
IMPAACT 2040, Phase I/II Pharmacokinetics, Safety, and Tolerability of Long-Acting Injectable Cabotegravir and Rilpivirine in People with Virally Suppressed HIV-1 during Pregnancy and Postpartum (CRAYON)	Rachel Scott, MedStar, United States Adrie Bekker, FAMCRU/Stellenbosch, South Africa
Concept 5032, Safety and Pharmacokinetics of Glecaprevir/Pibrentasvir (GLE/PIB) in Pregnant Persons with Hepatitis C with or without HIV	Proposed: Ahizechukwu Eke, JHU, United States Nathan Furukawa, CDC, United States
CAP 554, Phase I Study of the Infectivity, Safety and Immunogenicity of two Recombinant, Live-Attenuated, Bovine/Human, Parainfluenza Virus Type 3 (B/HPIV3) Vector Vaccines Expressing the Fusion Glycoprotein of Respiratory Syncytial Virus (RSV) Engineered for Increased Immunogenicity, Delivered in Single Doses as Nose Drops to HPIV3-Seronegative Infants and Children 6 to 18 Months of Age	Proposed: Coleen Cunningham, Univ California, Irvine, United States Elizabeth (Betsy) McFarland, Univ Colorado Denver, United States

Additional Resources

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DAIDS and NICHD

- Developing protocols: https://rsc.niaid.nih.gov/networks-protocol-teams/developing-protocols
- SCORE manual, in particular, *Introduction to DAIDS Systems*: https://www.niaid.nih.gov/research/daids-score-manual
- Manual for EAE Reporting to DAIDS: https://rsc.niaid.nih.gov/clinical-research-sites/manual-expedited-reporting-adverse-events-daids
- Grading Tables: https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables
- DAIDS and NICHD Medical Officers

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IMPAACT Central Resources

- Network Manual of Procedures: https://www.impaactnetwork.org/resources/manual-procedures
- Staff from the Network Central Resources (Clinical Research Managers, Statisticians, Protocol Data Managers, Laboratory Center representatives)
- Network Chairs and Vice Chairs

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THANKS!

Any questions?

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