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2023 CDISC TMF INTERCHANGE

BALTIMORE | 28-29 SEPTEMBER

Clinical - Regulatory Interoperability: A World of Opportunity

Meet the Speaker

Kathie Clark

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Organization: Ennov Software for Life

- Kathie is Ennov's Product Director for eTMF and CTMS. In addition, she has a background in Regulatory EDMS, submission publishing, Regulatory Information Management, and Quality Management. She has worked with life sciences organizations around the world for over 25 years, including working with FDA eCTD reviewers while working for GlobalSubmit. She is proud to be a member of the TMF Reference Model steering committee.

Disclaimer and Disclosures

- *The views and opinions expressed in this presentation are those of the author(s) and do not necessarily reflect the official policy or position of CDISC.*

- *The author has no real or apparent conflicts of interest to report.*

Agenda

1. Expected Benefits of Clinical - Regulatory Interoperability
2. Use Case Summary
3. Use Case 1: Protocol Amendment
4. Use Case 2: New Investigator
5. Use Case 3: Clinical Study Report Preparation and Publishing
6. Summary

Expected Benefits of Regulatory-Clinical Unification

Single Source of Truth

- Harmonize product information – single source
- Improve data quality and reliability
- Provide quick access to data for all stakeholders

Efficiency / Productivity Gains

- Eliminate repeated entry of data
- Decrease “clean up”
- Avoid need to monitor for changes

Compliance

- Enforce controlled vocabulary
- Provide traceability of information exchange
- Anticipate and track adherence to required deadlines

Risk Reduction

- Eliminate missed handoffs and late or missed filings
- Avoid inconsistencies
- Improve inspection outcomes

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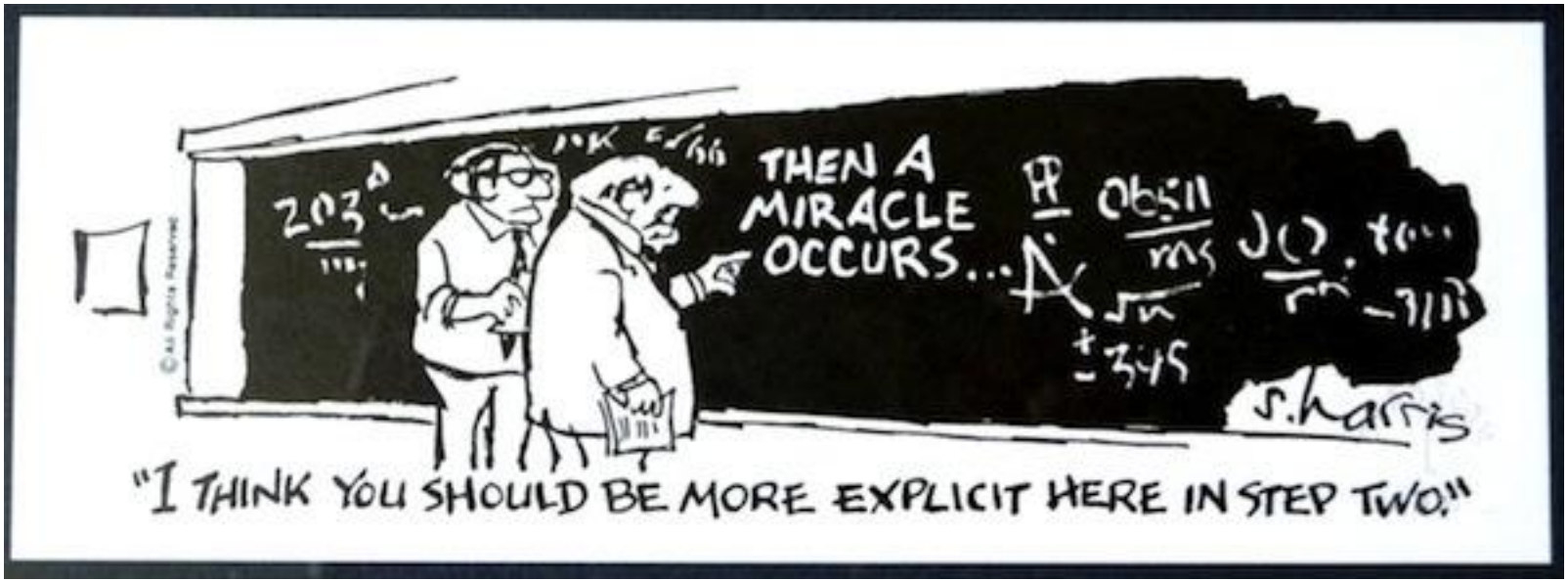
Clinical – Regulatory Unification: Not Just "Buy the Right Software and You Are Done!" (or "We've Got APIs")



Important Unification Use Cases

Example 01

New Protocol

Protocol written and reviewed; shared with sites; training conducted and recorded in training records. Protocol submitted to HAs and authorization obtained.

example 02

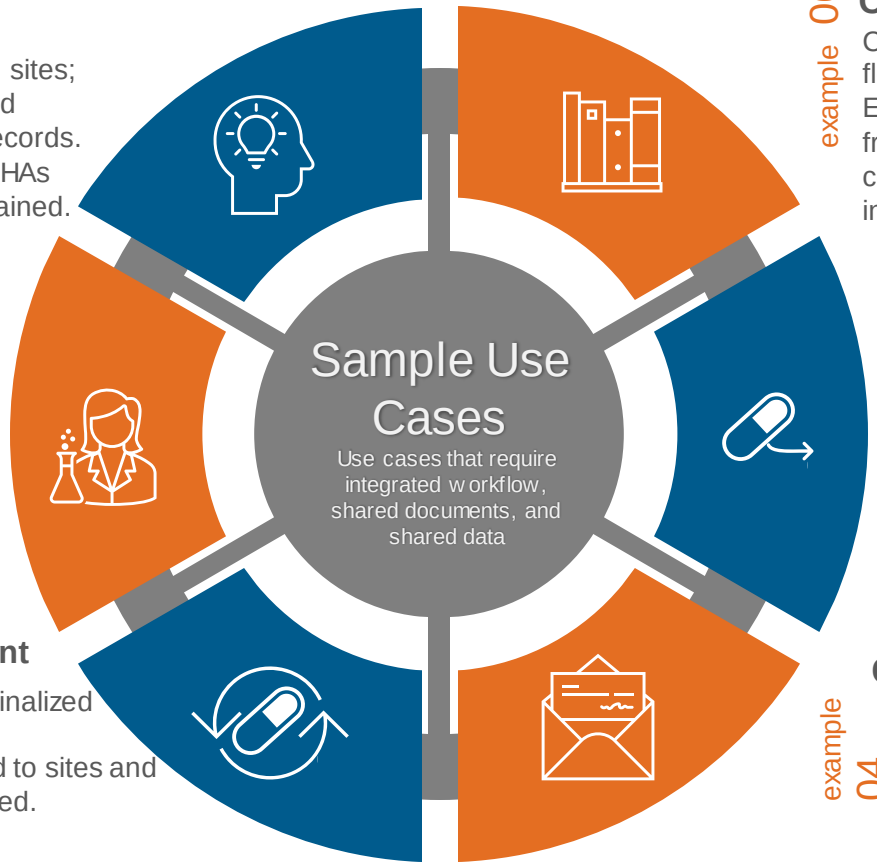
New Investigator

Investigator identified and documents collected; investigator published in IND amendment and sent to HA.

example 03

Protocol Amendment

Amendment planned, finalized and submitted to HA.
Amendment distributed to sites and documents and collected.



example 04

Correspondence

CTMS information alerts Reg Ops that updates are needed, XML extracted and submitted, .

example 05

ClinicalTrials.gov

CTMS updates result in alerts that updates are needed, XML extracted and submitted.

example 06

CSR Publishing

Case report forms and datasets flow from EDC to eTMF to Reg EDMS, lists of sites and IRBs from CTMS to dashboard, completed study report available in eTMF.

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Use Case Summary (1 of 2)

Use Case	Actions
New Protocol	• Alert to all impacted parties • Availability of document in eTMF and Regulatory EDMS • CTMS tasks to distribute to sites • Collection of signature pages, IRB approvals, etc. and etc. in eTMF • Submission of protocol in IND sequence or by other means outside the US • Link to IND sequence in eTMF when available; report of submission date and (depending on HA) approval or authorization
New Investigator	• Placeholders for documents created in eTMF; documents collected and finalized • Availability of CV and 1572 in Regulatory EDMS when finalized in eTMF • Alert and task for submission to Health Authority • Upcoming and Overdue submission info on dashboards in eTMF, RIM • Submission in IND sequence • Link to IND sequence in eTMF when available

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Use Case Summary (2 of 2)

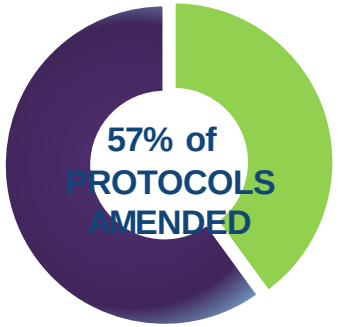
Use Case	Actions
Amended protocol, Investigator Brochure, etc.	• Alert to all impacted parties • Availability of document in eTMF and Regulatory EDMS • CTMS tasks to distribute to sites • Collection of signature pages, IRB approvals, etc. and etc. in eTMF • Submission in IND sequence • Link to IND sequence in eTMF when available
Correspondence	• HA correspondence related to trial synchronized; alerts issued
Clinicaltrials.gov / EudraCT support	• CTMS triggers RIM alerts dashboards when updates needed • XML produced • Submission dates updated
Clinical Study Report preparation and publishing	• Relevant eTMF documents (e.g. investigator CVs, sample CRF, patient CRFs) finalized in eTMF and available in Regulatory EDMS • Various information from CTMS used to create study report • Final CSR completed in Regulatory EDMS and available in eTMF; distributed to sites • Link to sequence containing CSR in eTMF

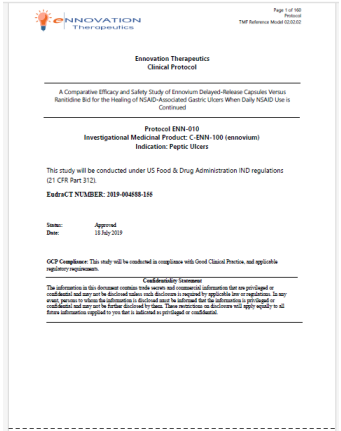
Protocol Amendment

Use Case 1

The Challenges: Responding to Change

"**57%** of protocols had at least one substantial amendment"




Ennovation Therapeutics
Clinical Protocol

A Comparative Efficacy and Safety Study of Ennovium Delayed-Release Capsules Versus Ranitidine Bid for the Healing of NSAID-Associated Gastric Ulcers When Daily NSAID Use is Continued

Protocol ENN-010
Investigational Medicinal Product: C-ENN-100 (ennovium)
Indication: Peptic Ulcers

This study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).

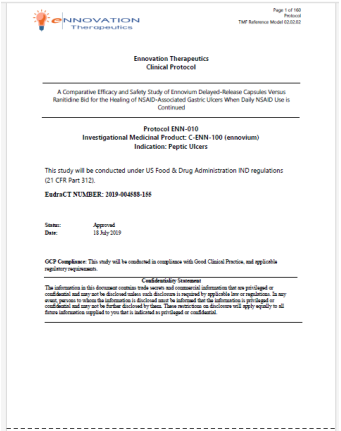
EndraCT NUMBER: 2019-004888-186

Status: Approved
Date: 18 July 2019

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

Confidentiality Statement

The information in this document contains trade secrets and commercial information that are privileged or confidential and may not be disclosed unless such disclosure is required by applicable law or regulations. In any event, persons to whom the information is disclosed must be informed that the information is privileged or confidential and may not be further disclosed by them. These restrictions on disclosure will apply equally to all future information supplied to you that is indicated as privileged or confidential.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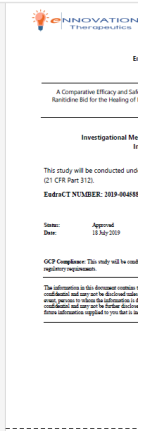

"Completed protocols across all clinical trials incur an average of **2.3** amendments."

Source: [The Impact of Protocol Amendments on Clinical Trial Performance and Cost]

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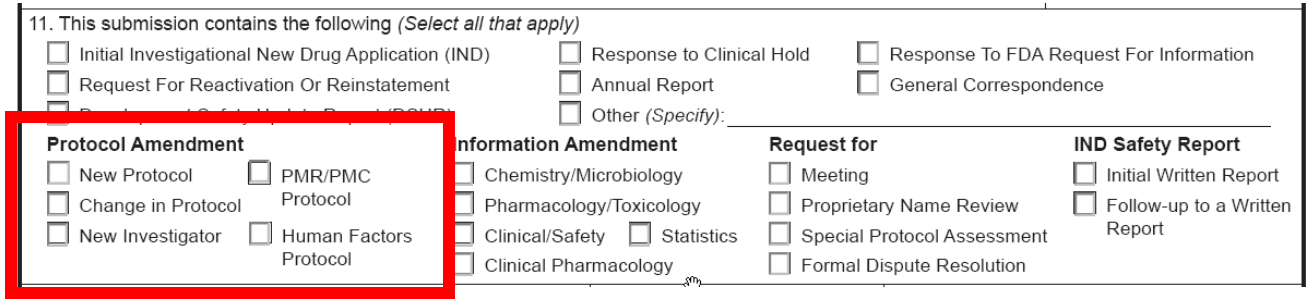
IND Application Reporting: Protocol Amendments

- Sponsors are expected to submit protocol amendments for new protocols or changes to existing protocols before implementation of changes.
- New studies may begin when the sponsor has submitted the change to FDA for its review and the new protocol or changes to the existing protocol have been approved by the IRB
- Therefore, Regulatory Affairs and Regulatory Operations need to:
  - Understand when a new protocol is approved internally and by IRBs
  - Submit in an IND Amendment (1571 below)



11. This submission contains the following *(Select all that apply)*

☐ Initial Investigational New Drug Application (IND)
☐ Request For Reactivation Or Reinstatement
☐ Response to Clinical Hold
☐ Annual Report
☐ Other *(Specify)*: _____
☐ Response To FDA Request For Information
☐ General Correspondence

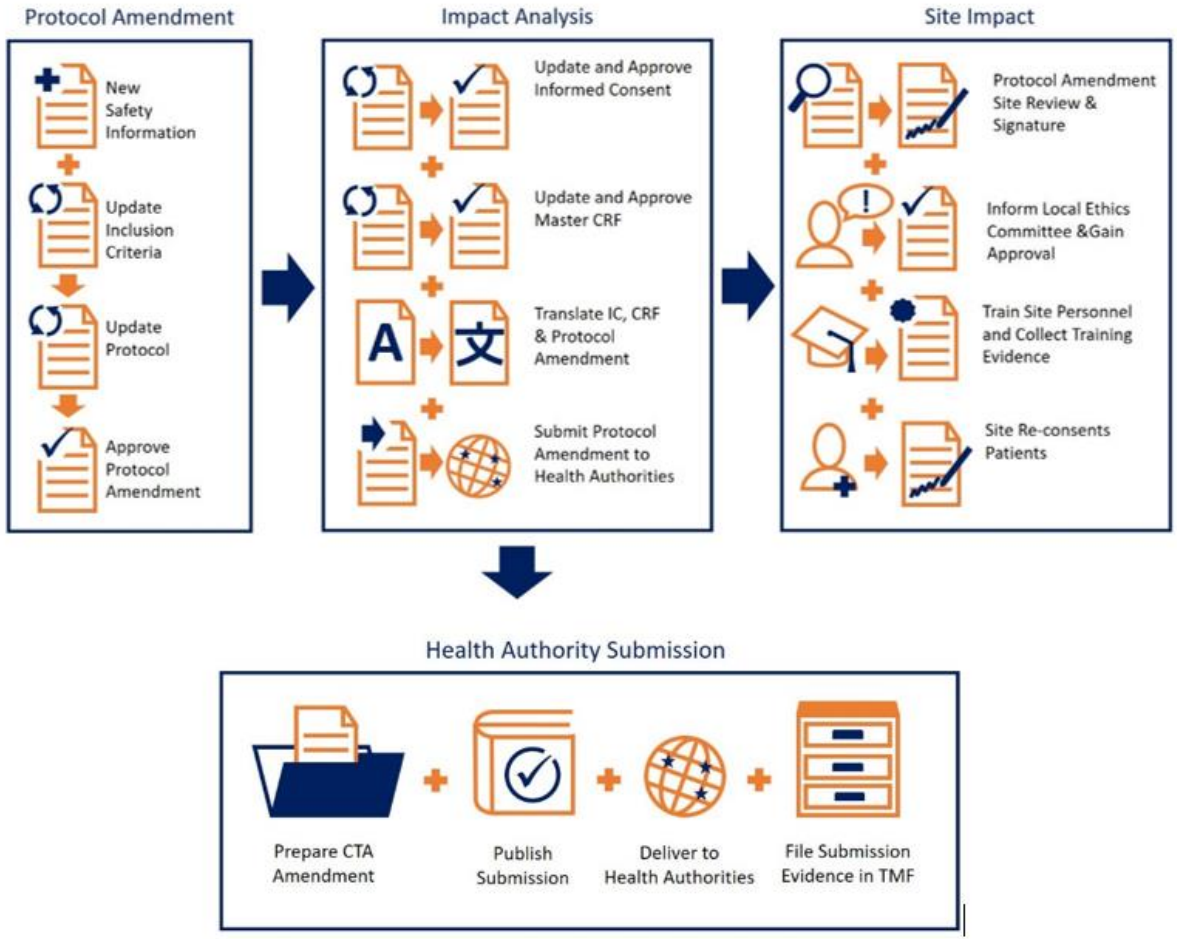
Protocol Amendment
☐ New Protocol
☐ Change in Protocol
☐ New Investigator
☐ PMR/PMC Protocol
☐ Human Factors Protocol

Information Amendment
☐ Chemistry/Microbiology
☐ Pharmacology/Toxicology
☐ Clinical/Safety
☐ Statistics
☐ Clinical Pharmacology

Request for
☐ Meeting
☐ Proprietary Name Review
☐ Special Protocol Assessment
☐ Formal Dispute Resolution

IND Safety Report
☐ Initial Written Report
☐ Follow-up to a Written Report

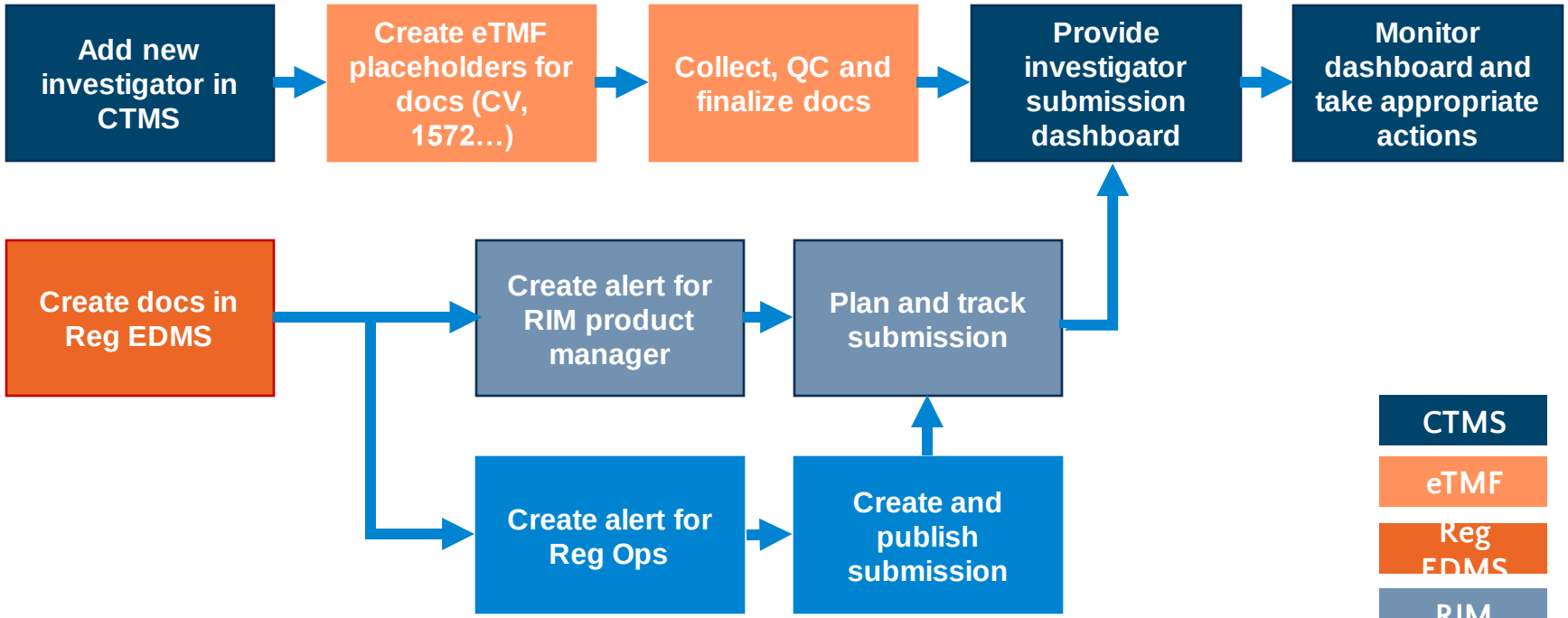
Managing Protocol Amendments



Document Management Challenges

- Taxonomy often very different between eTMF (TMF Reference Model) and Regulatory EDMS (EDM Reference Model or custom)
- Metadata needs vary for regulatory and clinical – but need to use the same master data (study IDs, indications, etc.)
- Documents often stored in different repositories and often manually replicated between them – resulting in version control challenges
- Some documents are the responsibility of the clinical team and some of the regulatory team
- Documents such as full regulatory submissions not needed in eTMF but may be needed by inspectors (who then need access to the regulatory EDMS)

Process Flow, Amendment



eTMF/CTMS Protocol Submission Status Dashboard: Single Trial

Protocol Submission Status: ENN-010

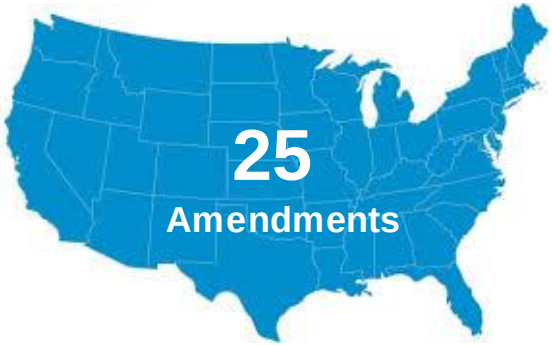
Protocol or Amendment	Date ↑	Market	Application	Submission Type	Sequence	Status	Date	Ethics Status
Protocol Amendment 1	10-Oct-2019	United States	076766	IND	0122	In Process		Incomplete
Protocol: A Randomized, Double-blind, Placebo-controlled, Single-dose, Dose-escalation Clinical Trial to Investigate the Safety, Tolerability, Pharmacokinetics, and Food Effect of Ennovium After Oral Administration in Healthy Male Volunteers	09-Oct-2018	United States	076766	IND	0077	Submitted	14-Nov-2018	Complete
Protocol: A Randomized, Double-blind, Placebo-controlled, Single-dose, Dose-escalation Clinical Trial to Investigate the Safety, Tolerability, Pharmacokinetics, and Food Effect of Ennovium After Oral Administration in Healthy Male Volunteers	09-Oct-2018	Canada	92812	CTA		Submitted	07-Jan-2019	Complete

- Bracketed info received back from Dossier / RIM
- Ethics Status leads to a separate view of IRB/IEC submissions and approvals

New Investigator

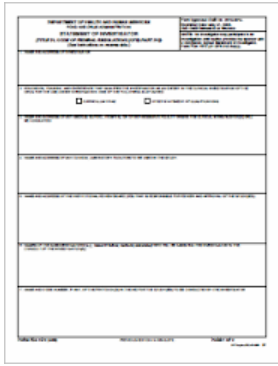
Use Case 2

The Challenges: Maintaining US INDs



Per year are typically filed for US INDs

INDs
contain an average of about
500
FDA Form 1572s
over the lifetime of the submission



FDA must be notified of a new principal investigator within **30 days** of them enrolling their first subject

IND Application Reporting: New Investigator

"*New investigator.* A sponsor shall submit a protocol amendment when a new investigator is added to carry out a previously submitted protocol, except that a protocol amendment is not required when a licensed practitioner is added in the case of a treatment protocol under § 312.315 or § 312.320.

Once the investigator is added to the study, the investigational drug may be shipped to the investigator and the investigator may begin participating in the study. The sponsor shall notify FDA of the new investigator within **30 days** of the investigator being added."

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Dashboard Card: New Investigators

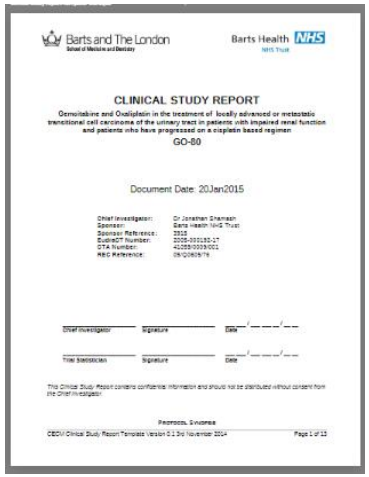
1. May want to be able to turn on/off for a study (if not under IND this may not be relevant)
2. Hyperlink the investigator name to the investigator object and list that investigator's documents under the object
3. Provide a control to show/hide already submitted investigators

Study	Site	Investigator	Date Added	Application	Sequence	Date Submitted	Alert
ENN-001	1027	Frazer, Mary	28-Aug-23				
ENN-001	1032	Ross, James	23-Aug-23	012345	0272	10-Sep-23	
ENN-001	2022	Bannerjee, Rahul	14-Aug-23	012345	0272	10-Sep-23	
ENN-005	1027	Diaz-Rodriguez, Sebastián	25-Jul-23				
ENN-005	4932	Anderson, Desiree	05-Jul-23	123902	0099	11-Aug-23	

Clinical Study Report Preparation and Publishing

Use Case 3

Medical Writing Challenges



Barts and The London School of Medicine and Dentistry

Barts Health NHS NHS Trust

CLINICAL STUDY REPORT

Gemcitabine and Oxaliplatin in the treatment of locally advanced or metastatic transitional cell carcinoma of the urinary tract in patients with impaired renal function and patients who have progressed on a cisplatin based regimen

GO-80

Document Date: 20Jan2015

Chief Investigator: Dr Jonathan Shamash
Sponsor: Barts Health NHS Trust
Sponsor Reference: 3515
EudraCT Number: 2005-001183-17
CTA Number: 4235/0039/001
REC Reference: 06/Q0605/76

Chief Investigator Signature Date

Trial Statistician Signature Date

This Clinical Study Report contains confidential information and should not be distributed without consent from the Chief Investigator.

Pharmacia, Sylvamed

CEDV Clinical Study Report Template Version 2.1 3rd November 2014 Page 1 of 13

....Optimally addressed by a combination of business process and technology

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- **Extracting data** from unstructured documents (e.g., opening many protocol deviations to extract the required information)
- Locating the **source of truth** for any given document or data element across disparate systems
- Ensuring the **latest version** of all resources is being used
- **Manual work** when information could be readily generated from electronic systems

Medical Writer Needs for Preparing CSR

1. Clinical data as tables, listings, and figures (TLFs)
2. Screening logs for subject disposition
3. Case report forms (CRFs) of subjects who had serious adverse events (SAEs)
4. Milestone study period dates: dates when first subject enrolled, last subject enrolled, and last subject completed
5. IRBs/IECs/DMC addresses and chairperson's name
6. Sample study-specific master Informed Consent Forms for protocol and all amendments
7. Study-specific case report forms (CRFs)
8. Safety (AE and/or SAE) narratives
9. Statistical Analysis Plan (SAP)
10. Pharmacokinetics (PK) report, if applicable
11. Pharmacodynamic report, if applicable
12. Toxicology report, if applicable
13. Immunogenicity report, if applicable
14. List of references (abstracts or manuscripts) from publications derived from clinical study data
15. Medical literature supporting the study and cited in the CSR
16. Original clinical study protocol and all amendments
17. Investigator brochure (versions used in the study)
18. Chairperson and address of DMC
19. List of site names, numbers, and locations
20. Company that managed the clinical trial supply
21. Names and addresses of laboratory facilities used
22. Lab certificates and normal ranges for all labs
23. Investigators' CVs
24. List of investigational drug batch numbers and list of subjects receiving each batch of IP
25. List of protocol deviations
26. List of investigators and study personnel, mailing and e-mail addresses, telephone and fax
27. List of names and contact information of sponsor's personnel who participated in the clinical study: medical monitor, biostatistician, and CRAs

eTMF CTMS Regulatory EDMS

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Summary

Summary and Recommendations

- Business Process
  - Ensure that all process flows, handoffs, and master data sources are identified
  - Tag correspondence related to clinical studies
  - Review where problems or delays have occurred in the past
  - Check that all reporting loops are closed
- Technology
  - Find out what your available tools can do - out of the box, by configuration, by integration, or not at all
  - Wherever possible, create reports and dashboards
    - Reports and dashboards for medical writers
    - IND sequences related to protocol submission, amendment and new investigators
    - Correspondence related to clinical studies
    - Changes reportable to ClinicalTrials.gov or other registries

Thank You!