JAPAN ACADEMIC WORKSHOP

Friday, 17 November | 1:00pm -5:15pm

Use of CDISC SDTM in large-scale individual participant data meta-analyses

Presented by Dr Christina Reith
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Meet the Speaker

Christina Reith

Title: Associate Professor

Organization: University of Oxford

Christina studied at The University of Glasgow in Scotland. She worked as a clinician in the UK, subsequently completing speciality training in Pharmaceutical Medicine in 2011.

Christina mainly works on large-scale clinical trials and meta-analyses in relation to cardiovascular disease, with a particular research interest being the reliable assessment of drug safety using such large-scale randomized data. She has worked closely on the Study of Heart and Renal Protection (SHARP), one of the largest ever trials in patients with moderate-to-severe chronic kidney disease, and is currently focused on individual participant data meta-analyses such as those conducted by the Cholesterol Treatment Trialists' (CTT) Collaboration.

She has an interest in streamlining clinical trial methodology, and worked with the Clinical Trials Transformation Initiative (CTTI), the Good Clinical Trials Collaborative (GCTC) and the World Health Organisation (WHO) in relation to clinical trials guidance.

In addition she is a Board Member for the Clinical Data Interchange Standards Consortium (CDISC).

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Need for individual participant data meta-analyses

- Recognised that often no single randomised controlled trial of an intervention has enough participants to enable reliable assessment of mortality outcomes or assess effects in particular types of patient

- Can address this by conducting individual participant data (IPD) meta-analyses of available RCTs

- IPD meta-analyses can be challenging:
  - more labour-intensive and complex than tabular meta-analyses; can take considerable time
  - in current era, data sharing agreements, anonymisation of data and use of data sharing platforms a consideration for IPD m-a

- Main current project: Cholesterol Treatment Trialists' (CTT) Collaboration: https://www.cttcollaboration.org/

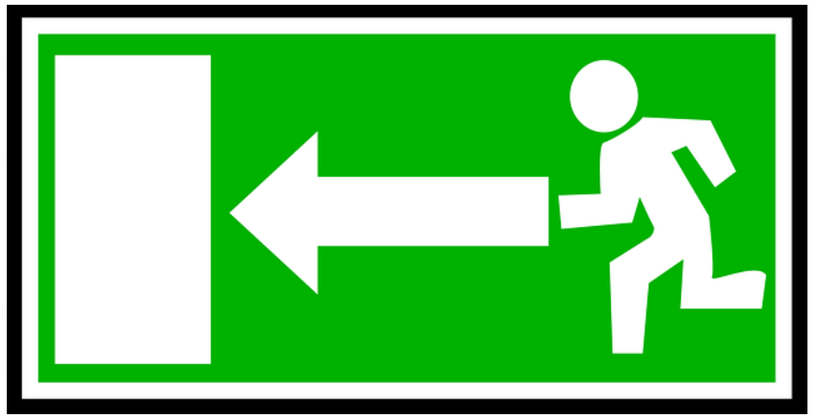
The Cholesterol Treatment Trialists' (CTT) Collaboration: Background

- Cholesterol Treatment Trialists' (CTT) Collaboration originally set up in early 1990s to assess effects of statins on major vascular outcomes, mortality and cancer (protocol Am J Cardiol. 1995 Jun 1;75(16):1130-4)
  - IPD meta-analysis from 28 statin trials with ≥1000 participants; ≥2 years scheduled follow-up: (~175,000 participants); showed statins highly effective in reducing risk of CVD: https://www.cttcollaboration.org/efficacy-web-page
  - one of most widely prescribed drugs worldwide; now generic
  - aim to address widespread concerns re. possible statin side effects fuelled by inaccurate media reports > uncertainty in patients and doctors SUBSTANTIAL PUBLIC HEALTH CONCERN
- Further project commenced 2016 (protocol: Am Heart J. 2016 Jun;176:63-9): extension of the CTT IPD dataset to encompass all recorded AEs for each of the participating trials
  - including reasons for stopping study treatment, co-meds, laboratory results

Data received for current CTT project

- Data from 23 double-blind statin trials and 5 open-label statin trials provided, either through direct data transfer or through online access portals
- Received protocols, statistical analysis plans, case report forms, clinical study reports, data sets
- Rapidly became clear this was not simple……
  - Use of data sharing platforms for some trials meant planned meta-analyses done using a ‘2-stage’ approach
  - LARGE! **845 datasets; > 38M records**, > 30K study variables, nearly 182K randomized patients; nearly 1.2 million adverse events (~45K unique terms)
  - MESSY! Substantial **inter-trial heterogeneity**, including multiple different languages used to code events (e.g. ICD9, ICD10 MedDRA and custom code)

What to do??



What to do??

Harmonisation of CTT data into single analysable database

- **2-pronged approach** deployed to create harmony out of heterogeneity
- Relevant baseline and follow-up data from each trial reorganised into standardised formats based upon the Clinical Data Interchange Standards Consortium Study Data Tabulation Model (**CDISC SDTM**)
    - Pragmatic streamlined approach adopted with just **13 out of the available 46 domains** considered sufficient
- Adverse event data organised and coded (automatically or, where necessary, manually) according to a common medical dictionary based upon the Medical Dictionary for Regulatory Activities (**MedDRA**)
- Methods published: Cholesterol Treatment Trialists' Collaboration. Harmonisation of large-scale, heterogeneous individual participant adverse event data from randomised trials of statin therapy. *Clinical Trials*. 2022;19(6):593-604. doi:10.1177/17407745221105509

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CDISC standards and IPD meta-analysis projects

Applicability of CDISC standards to CTT:

- CDASH
  - Trials already completed (often years ago)
- SDTM
  - Useful but with some modifications
- ADaM
  - Less easily deployed if not already used CDASH and SDTM

Use of standards like SDTM in CTT: advantages

- Provides standard structure for organizing and formatting data
- Available SDTM domains broadly encompassed range of data types required for CTT
- Using recognisable standard beneficial for:
  - Sharing/transparency of methods
  - Audit purposes
  - ‘Future proofing’ (projects like CTT run for many years)

SDTM: Modelled domains (SDTMIG v3.2)

Interventions
Conmed
Exposure
Substance use
Exposure as collected
Procedures

Events
Adverse events
Disposition
Medical history
Deviations
Clinical events
Health care encounters

Findings	
ECG	Death Details
Inclusion/Exclusion Criteria Not Met	Immunogenicity
Labs	Microscopic Findings
Physical Exam	Morphology
Questionnaire	Reproductive System Findings
Subject Characteristics	Subject Status
Vital Signs	Tumour Identification
Drug Accountability	Tumour Results
Microbiology Specimen	Disease Response
Microbiology Susceptibility	
PK Concentrations	
PK Parameters	
Findings About	

Findings About
Findings About
Skin Response

Special Purpose
Demographics
Comments
Subject Elements
Subject Vitals

Relationships
SuppQual
Relrec

Trial Design
Trial Elements
Trial Arms
Trial Visits
Trial Inclusion/Exclusion Criteria
Trial Summary
Trial Disease Assessments

SDTM domains used by CTT

Interventions

- Conmed
- Exposure
- Exposure as collected
- Procedures
- Substance use

Events

- Adverse events
- Clinical events
- Disposition
- Healthcare encounters
- Medical history
- Protocol Deviations

Findings

- Death Details
- Disease Response
- Drug Accountability
- ECG
- Immunogenicity
- Inclusion/Exclusion Criteria Not Met
- Labs
- Microbiology Specimen
- Microbiology Susceptibility
- Microscopic Findings
- Morphology
- Physical Exam
- PK Concentrations
- PK Parameters
- Questionnaire
- Reproductive System Findings
- Subject Characteristics
- Subject Status
- Tumour Identification
- Tumour Results
- Vital Signs

Findings About

- Findings About
- Skin Response

Special Purpose

- Demographics
- Comments
- Subject Elements
- Subject Visits

Relationships

- Supplemental Qualifiers
- Related records

Trial Design

- Trial Arms
- Trial Disease Assessments
- Trial Elements
- Trial Inclusion/Exclusion Criteria
- Trial Summary
- Trial Visits

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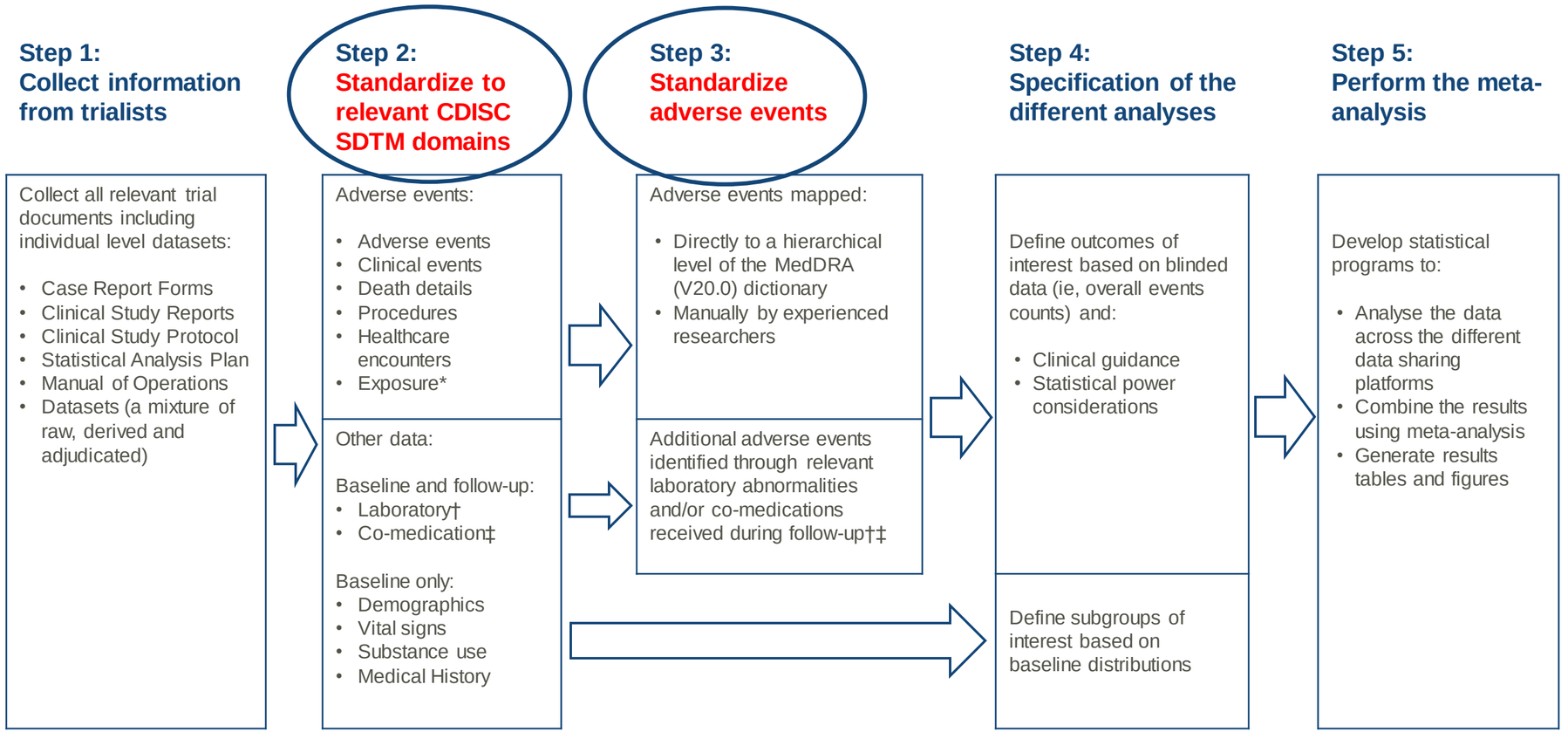
What if trials had already used SDTM?

- In CTT, due to vintage of contributing trial data, only 2 trials (conducted by our department: HPS and SEARCH) came in SDTM format; simplified work
- However, such ‘retrofitting’ of already published trial data to SDTM a considerable amount of effort
- Likely not realistic to expect all historic trial data to be converted to SDTM

Summary of CTT data processing



Summary

- Some aspects CDISC may only work for individual trials commenced in the CDISC era
- However, modified version of CDISC SDTM can be successfully used for ‘big data’ projects across multiple highly heterogeneous legacy datasets
- Such use of CDISC SDTM likely underutilised
- Need to make such examples accessible
- CTT methodology paper published
- Still requires substantial resource, so need well thought out and pre-specified question

Acknowledgements

- All patients who took part in the original trials included in the CTT project
- Collaborating trialists
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- CTT Independent Oversight Committee: E Banks, M Blastland, S Evans, R Temple, P Weissberg (chair), J Wittes
- NDPH Communications team

Thank You!

More information:

- https://www.cttcollaboration.org/
- Cholesterol Treatment Trialists' Collaboration. Harmonisation of large-scale, heterogeneous individual participant adverse event data from randomised trials of statin therapy. *Clinical Trials*. 2022;19(6):593-604. doi:10.1177/17407745221105509
- Results re statin effects on muscle outcomes:
  - Lancet 2022; 400; 832-45
  - https://www.cttcollaboration.org/news/new-study-muscle-pain