Contacting authors to retrieve individual patient data: a randomized controlled trial

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I have no actual or potential conflict of interest in relation to this presentation

Learning Objectives

- To increase knowledge about what an IPD (network) meta-analysis (NMA) is
  - When an IPD-NMA may be preferred vs. an aggregated data NMA?

- To discuss the importance of patient level data and challenges associated with obtaining it

- To examine the impact of providing incentives to authors of RCTs when requesting IPD

Clinical trials

Comparison of 2 treatment groups

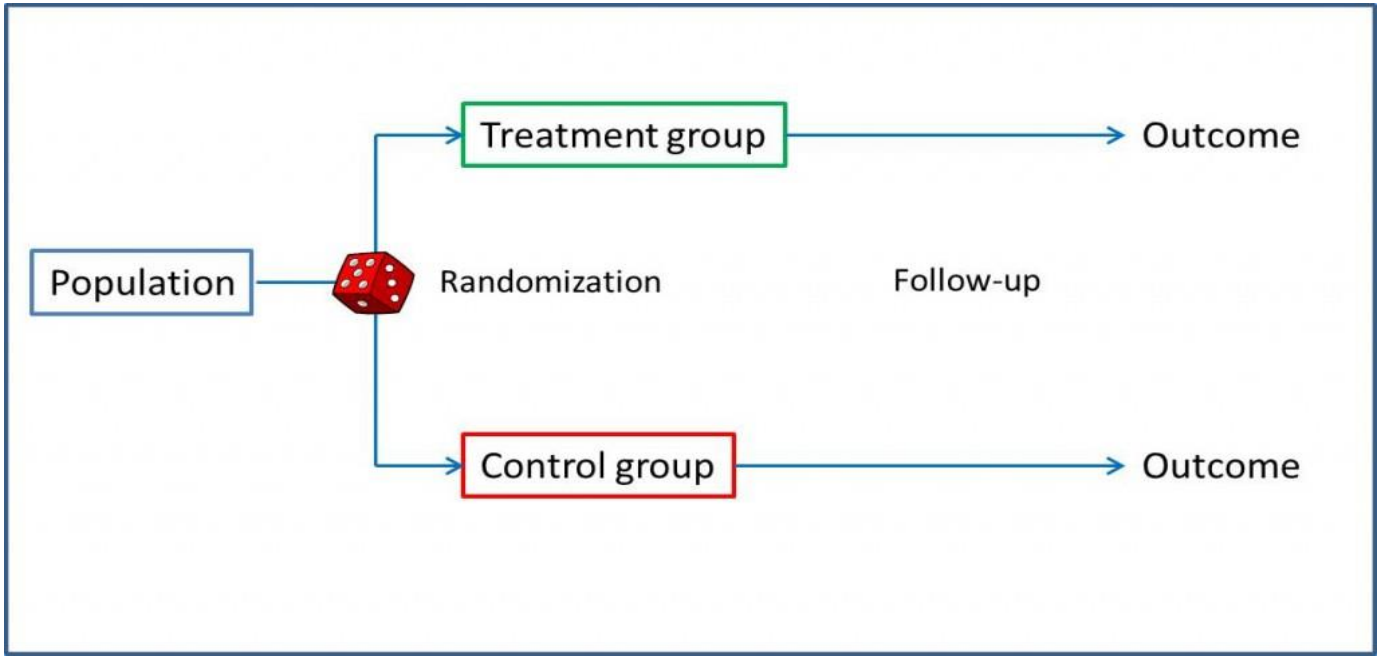
Treatment Group (e.g., granisetron)

Control Group (e.g., placebo)

Which treatment is more effective?

Randomized clinical trials (RCTs)

A clinical trial in which the participants are assigned randomly (by chance alone) to different treatments

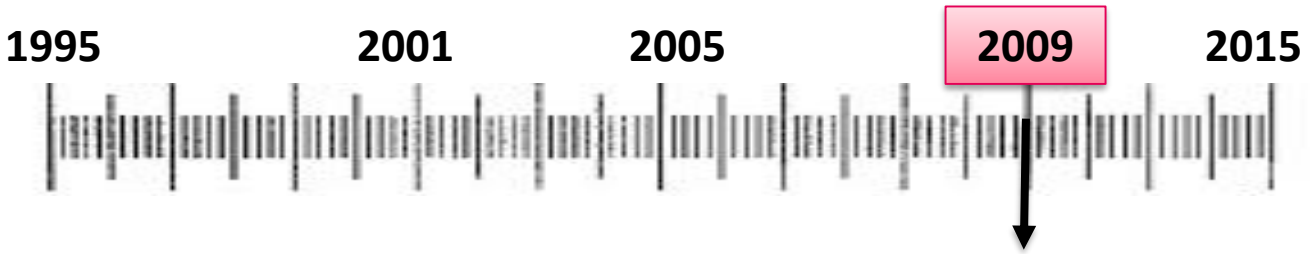


By chance, all characteristics will be on average the same in the two groups

Clinical decision making

Serotonin 5-hydroxytryptamine 3 (5-HT3) receptor antagonists to relieve nausea in patients undergoing surgery

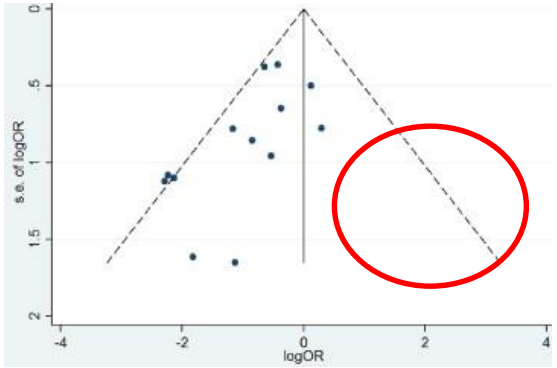
- Multiple RCTs were needed to approve granisetron in Canada
- 21 RCTs, including 1,963 patients in total, have been conducted since 1995
- The synthesis of the results of these RCTs showed a statistically significant reduction in nausea



Why did it take us so long?

Because …

- The results of individual studies are not always sufficient to draw conclusions, as studies may be:
  - Small and imprecise; low power
  - Biased
  - Missing; not all studies are published and available (e.g., journals tend to publish research with positive and interesting findings)



Why did it take us so long?

Because …

- The results of different studies may vary
  - Studies may suggest contradicting results
  - We cannot always be certain that the observed differences across studies are due to chance
- Not all questions of interest are posed by the individual studies and further exploration may be needed

*"**Granisetron** tends to have a favorable trend in response rates compared with **Ondansetron**"*

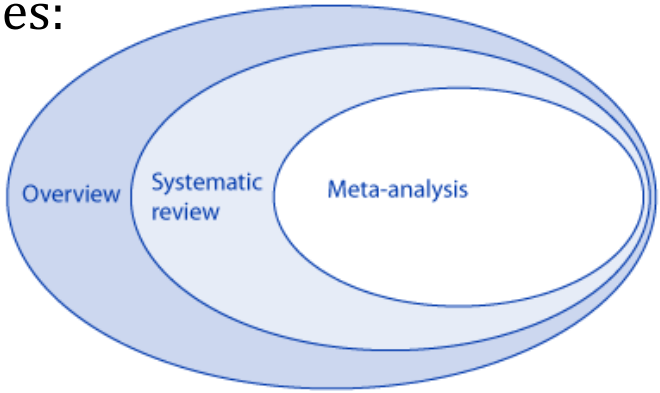
*"The results indicate that **Granisetron** was significantly better than **Ondansetron**."*

*"**Granisetron** showed similar efficacy compared with **Ondansetron**,"*

How can we improve clinical practice?

- Systematic reviews and meta-analyses attempt to:
  - identify all relevant studies fulfilling predefined criteria
  - systematically summarize the validity and findings of the studies
  - synthesize or integrate the findings
  - improve understanding of the vast amount of information
  - improve clinical practice and future research

- Rationale for systematic reviews and meta-analyses:
  - Minimise bias
  - Enhance precision
  - Put results into context



Aggregate Data (AD) Meta-analysis

AD meta-analyses: use summary point estimates from all patients enrolled in each included trial

- Data are not available on individual patients

Treatment	Granisetron		Placebo	
Study	# of Events	# of Patients	# of Events	# of Patients
1	4	50	37	50
2	1	35	20	45
3	1	17	18	34
4	6	158	141	158
5	8	267	437	504
6	88	112	67	120
7	0	57	15	70
8	3	27	4	30
9	13	150	15	140
10	0	49	20	70
11	15	71	2	80
12	0	87	128	181
13	0	89	136	178

Aggregate data meta-analysis

- May suffer from relatively low statistical power
- It is challenging to:
  - Harmonize variable definitions
  - Harmonize inclusion and exclusion criteria
  - Combine studies with different follow-up times
  - Adjust for study-specific biases (e.g. aggregation bias)
  - Explore sources of between-study heterogeneity (e.g. due to treatment-covariate interactions)

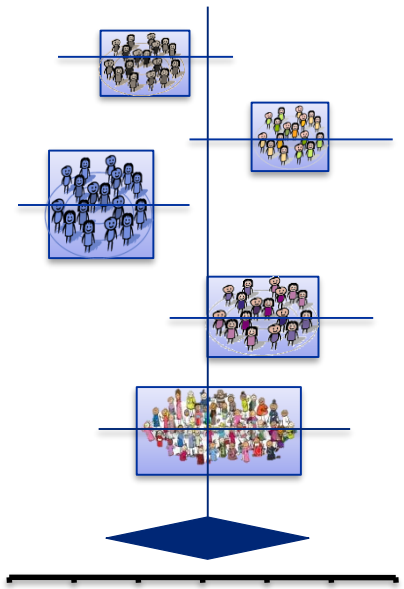
Individual Patient Data (IPD) Meta-analysis

IPD meta-analyses: use data from each individual patient enrolled in each included trial

- Allows similar analysis across all trials
- Allows investigation of patient-level moderators

	A	B	C	D	E	F	G
1	Study	StudyID	ParticipantID	InterventionCode	BinaryOutcome	age	gender
2	CAR001	1	1	Granisetron	Vomit	23	woman
3	CAR001	1	2	Placebo	No Vomit	24	woman
4	CAR001	1	3	Granisetron	No Vomit	43	man
5	CAR001	1	4	Granisetron	No Vomit	22	man
6	CAR001	1	5	Granisetron	No Vomit	39	man
7	CAR001	1	6	Granisetron	No Vomit	21	man
8	CAR001	1	7	Granisetron	No Vomit	37	man
9	CAR001	1	8	Granisetron	No Vomit	37	man
10	CAR001	1	9	Granisetron	No Vomit	19	man
11	CAR001	1	10	Placebo	Vomit	39	man
12	CAR001	1	11	Placebo	Vomit	23	woman
13	CAR001	1	12	Placebo	Vomit	22	woman
14	CAR001	1	13	Placebo	No Vomit	43	woman
15	CAR001	1	14	Placebo	No Vomit	28	woman

AD vs. IPD (network) meta-analysis

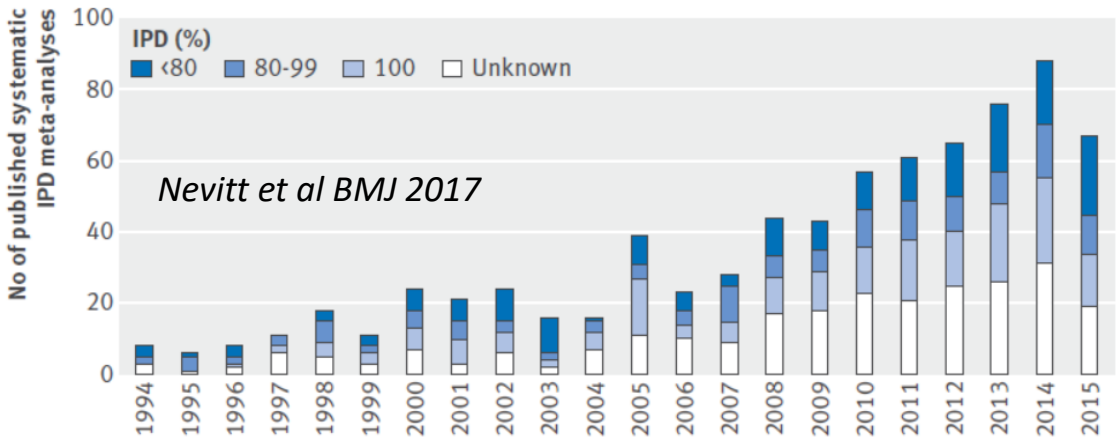


- IPD meta-analysis is the gold standard for synthesising evidence across clinical trials
- AD and IPD models can be equivalent if data & effect sizes are equivalent
  - Discrepancies arise because IPD data sets include different data than AD (e.g. may reinstate patients originally excluded, additional follow-up data)
- IPD meta-analysis in soft tissue sarcoma: 24% of patients were excluded in the treatment arm compared with 20% in the control arm – 99% of excluded patients were recovered
  - Meta-analysis with exclusions: HR=0.85 (p=0.06)
  - Meta-analysis reinstating all exclusions: HR=0.90 (p=0.16)

Tierney and Stewart Int J Epidemiol 2005

- Empirical evidence suggests AD models might be misleading for the evaluation of the prerequisite NMA assumptions

Donegan et al Stat Med 2012



AD vs. IPD (network) meta-analysis

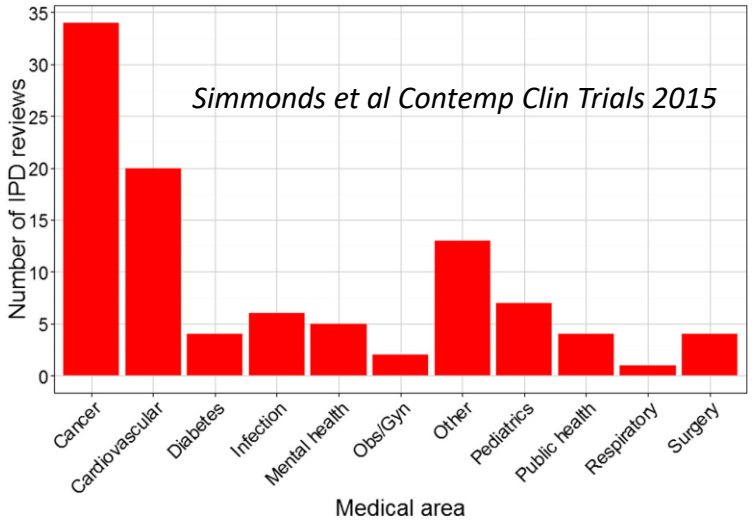
Individual patient data meta-analysis (IPD-MA)

- ✓ Includes checks to ensure homogeneity, quality of randomization, and follow-up analysis
- ✓ Overcomes outcome reporting bias
- ✓ Increases precision
- ✓ Uses consistent inclusion/exclusion criteria across studies
- ✓ Allows participant-level covariates to be directly modeled, increasing statistical power and detects participant-treatment relationships if they are present
  - Answers what interventions are most effective in:
    - men versus women
    - older people versus younger people

☒ Is time-consuming and costly

- A previous IPD-MA of 19 studies required:
  - 4 research coordinators (RCs) investing 5-20% of their full time
  - 2,088 hours of data management
  - More than 1000 emails between the RCs and IPD authors

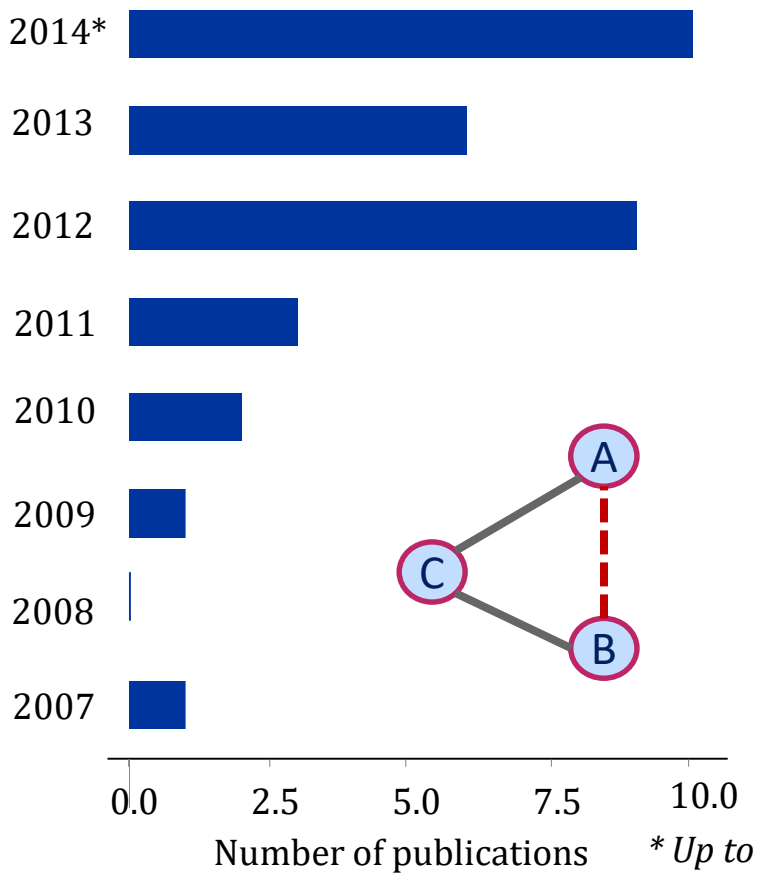
Ioannidis et al Am J Epidemiol. 2002



☒ May not be able to obtain all IPD = retrieval bias

IPD in indirect comparisons

IPD indirect comparisons are published with increasing frequency in health care literature



"...the balance of gains and losses of the approach will vary according to the disease, treatment, and therapeutic questions explored"

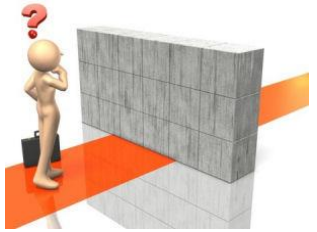
Stewart and Tierney Eval Health Prof 2002

- 30% studies of the 33 empirical networks were able to obtain IPD for all studies
- 67% studies of the 33 empirical networks identified IPD from a collaborative group
- 46% studies of the total 37 articles were industry-sponsored

** Up to October 2014*

Veroniki et al BMC Med Res Methodol 2016

Barriers to data sharing



Examples of barriers…

- Author's response from a published RCT, where the PI worked at the National Institutes of Health (NIH) and the study was federally funded: "*We are not prepared to release the data at this point.*"
- RCT corresponding author: "*Would love to share the data, but my biostatistician won't release it*"
- PI agrees to provide data, but the PI fails to get approval from the co-investigators
- "*Analytical methods are pre-specified in study protocols and it is inappropriate to use other methods*"
- Contacting a physician at a Cancer Center involved: 1) extended discussion, 2) subsequent 45 minute telephone conference, 3) present a written proposal, 4) no reply

Challenges

Vickers Trials 2006

- Clinical trialists may
  - Be concerned with being scooped and with misrepresentation of their work
  - Worry that a re-analysis might show an error or a pattern they missed
  - Have limited publication rights for the data as a study sponsor owns them
  - Have moved to a different university and lost the data
  - Do not have access to the data (old data or data saved in an inaccessible storage device)

Sharing IPD from RCTs

- **Possible solutions:**
  - Include original trialists as co-authors
  - Offer the opportunity to trialists to read, revise papers before submission
  - Contact the lead and last authors of the paper together, send reminders, and if no response try other listed authors
  - Match up authors with clinicians/researchers you know and set up face-to-face meetings
  - Attend clinical conferences coming up where you can present your study and make a pledge for data of the relevant trials (either as a presentation or by networking)
  - Attempt to contact the statisticians (perhaps they will nudge their co-authors)
  - Look on clinicaltrials.gov or other registries to find contact details

- However, missing data and publication bias distort the medical literature and harm patients when erroneous decisions are made
  - Many RCTs are not published within a reasonable time after completion or are never published at all.
  - IPD meta-analyses based only a portion of the trials that were conducted (either by failing to identify them or by using a subset of existing studies on purpose) can affect the results in unknown and unpredictable ways

Ahmed et al BMJ 2012; Flegal & Ioannidis JCE 2017; Nevitt BMJ 2017; Veroniki et al Trials 2016; Vickers Trials 2006

Whose data set is it anyway?

Do the data belong to the patients who comprise it or the investigators?

- The data legally belong to trialists on the grounds that it requires work to create knowledge from data
- But science, is essentially an enterprise conducted for moral reasons
- We rely on evidence-based medicine to give us reliable information about the risks and benefits associated with medical interventions, but evidence indicates that the medical literature is not always reliable

Examples of failing to report safety and effectiveness of drugs:

- Influenza antiviral Tamiflu (oseltamivir)
  - Many governmental bodies assumed the drug would reduce the complications of influenza, and hospitalizations, based on a Roche supported meta-analysis
  - This claim was challenged by a 2009 Cochrane review update - detected numerous reporting biases and fundamental problems in trial design; previous effectiveness claims were not supported by the available evidence
  - After serious concerns were voiced in the BMJ about Tamiflu, Roche said they would share the data with “appropriate” authorities or individuals
  - There was a public call for IPD to be made publicly available, but in the end Roche refused to share full reports with multiple reasons for not providing these data cited

Whose data set is it anyway?

Examples of failing to report safety and effectiveness of drugs:

- Nonsteroidal anti-inflammatory Rofecoxib (Vioxx; Merck)
  - Unexpected and unanticipated cardiovascular events (principally, myocardial infarction). Increased cardiovascular disease risk
  - Merck had data several years before Vioxx was withdrawn from the market that showed the drug increased the risk of heart attacks, but most of the data were unpublished and not publicized
  - Some of the Vioxx related deaths might have been avoided had Merck been forced to publish raw data on individual patients

- Antidiabetic Rosiglitazone (Avandia; GSK)
  - 2005–2007 series of meta-analyses increasingly suggest harms, especially cardiovascular
  - The primary trials used methods with several limitations, including excessive loss to follow-up, and over-emphasis on proxy outcome measures (blood glucose levels rather than mortality and morbidity outcomes)
  - Public disclosure of unpublished study results was critical to uncovering the evidence of harm

Doshi et al PLoS Med 2012

Whose data set is it anyway?

Examples of failing to report safety and effectiveness of drugs:

- Clinical trials are published but the data are reported in a misleading and biased way, as when a negative trial is presented so as to appear positive or analyses showing harm are omitted.
  - Selective Publication of Antidepressant Trials (Turner et al NEJM 2008)

What is to be done?

- Make data publicly available
  - After completion of studies, de-identify and make data globally available –(see https://metrics.stanford.edu/research)
- Bring data sharing and open science into the mainstream of clinical research
- Post, in the public domain, the study protocol for each trial
- Encourage industry to commit to place all its clinical data relevant to approved products in the public domain

- Identify trials that are not published (e.g., use www.clinicaltrials.gov) to determine what is missing

https://marilynmann.net/category/data%ADsharing/5/7

What is to be done?

Benefits

- Reproducing analyses
- Testing secondary hypotheses
- Developing and evaluating novel statistical methods
- Teaching
- Aiding design of future trials
- Meta-analysis
- Preventing error, fraud and selective reporting

Vickers Trials 2006

BUT: many obstacles — political, cultural, financial — to accomplishing these goals.

- Whatever the difficulties, patients deserve reliable information on the risks and benefits of medical treatments and the subjects of clinical trials deserve that their contributions be fully used to benefit other patients

Knowledge about the effectiveness of interventions in different subgroups of patients is particularly important for clinical decision making!

When IPD may help shed light on the results?

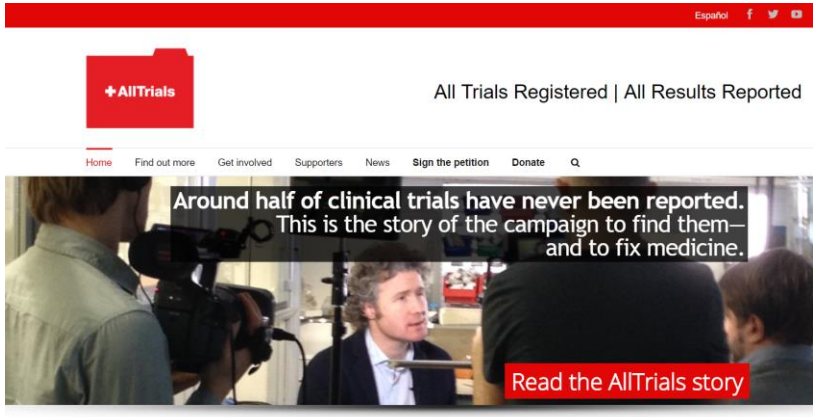
TABLE 2
Factors That May Influence the Systematic Review Approach

When Individual Patient Data May Be Beneficial	*When Individual Patient Data May Not Be Beneficial*
Poor reporting of trials: Information inadequate, selective, or ambiguous	Detailed and clear reporting of trials (CONSORT quality)
Long-term outcomes	Short-term outcomes
Time-to-event outcome measures	Binary outcome measures
Multivariate or other complex analyses	Univariate or simple analyses
Differently defined outcome measures	Outcome measures defined uniformly across trials
Subgroup analyses of patient-level characteristics important	Patient subgroups not important
Individual patient data available for high proportion of trials/individuals	Individual patient data available for only a limited number of trials

Stewart, Tierney Evaluation & the Health Professions 2002

Initiatives to encourage data sharing

- Medical journals have attempted to deal with this difficulty by endorsing standards for reporting of study results (CONSORT)
- A number of consortia have been formed to share IPD
  - e.g., Psychiatric GWAS Consortium Steering Committee, 2009; Evangelou & Ioannidis, 2013; Lin et al., 2013
  - International initiative AllTrials: http://www.alltrials.net/
  - The Clinical Study Data Request (CSDR) System: https://www.clinicalstudydatarequest.com/
  - The Yale University Open Data Access (YODA) Project: http://yoda.yale.edu/



- Although, there has been an improvement in access and awareness towards data sharing, the IPD retrieval rate has *not* improved over time

Nevitt BMJ 2017

Initiatives to encourage data sharing

- Empirical evidence shows that
  - Of the 760 IPD meta-analysis published between 1987 and 2015 only 188 (25%) IPD-MA retrieved 100% of the eligible IPD!
  - Higher IPD retrieval rates were associated with IPD meta-analyses of RCTs, an authorship policy (individual authorship for those providing IPD, or collaborative group), trials of fewer participants, non-Cochrane reviews
  - Reported reasons for lack of data availability have changed in recent years - most common reason for not being able to retrieve data for academic trials was because of failure to contact data providers
- The strong movement to share anonymized IPD has not been well established yet
  - A planned IPD meta-analysis in 2014 failed to be conducted, as the majority of the primary study authors did not share their data
- The cooperation of the original study authors is crucial for providing the data in a usable format and answering queries about their data
- Efforts need to be undertaken to understand how to optimize the data sharing process

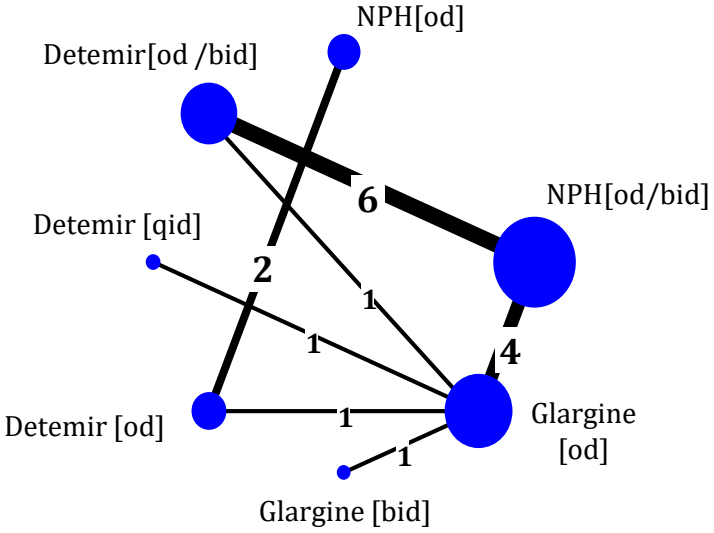
Jaspers et al Syst Rev. 2014; Nevitt et al BMJ 2017

Network meta-analysis using IPD

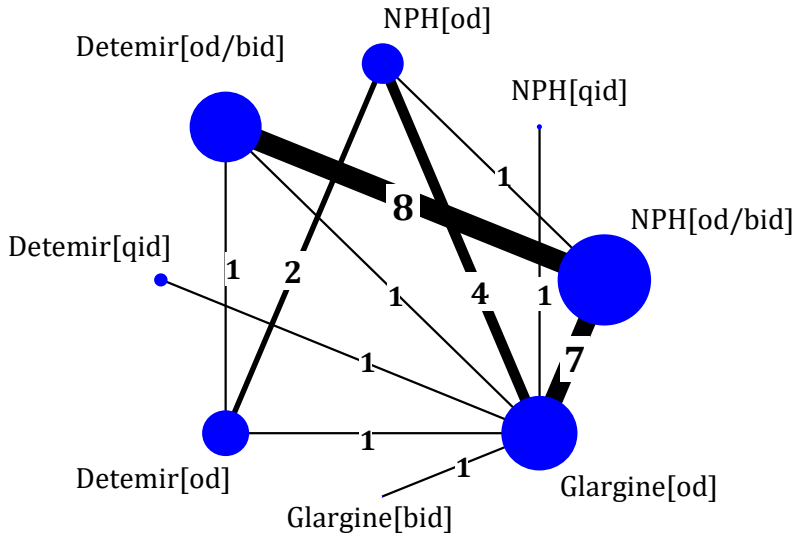
Safety and effectiveness of long-acting versus intermediate-acting insulin for patients with type 1 diabetes mellitus (T1DM)

Tricco et al BMJ 2014;349:g5459

Severe Hypoglycemia



Baseline glycosylated hemoglobin (A1C)



Veroniki et al BMJ Open 2015;5:e010160

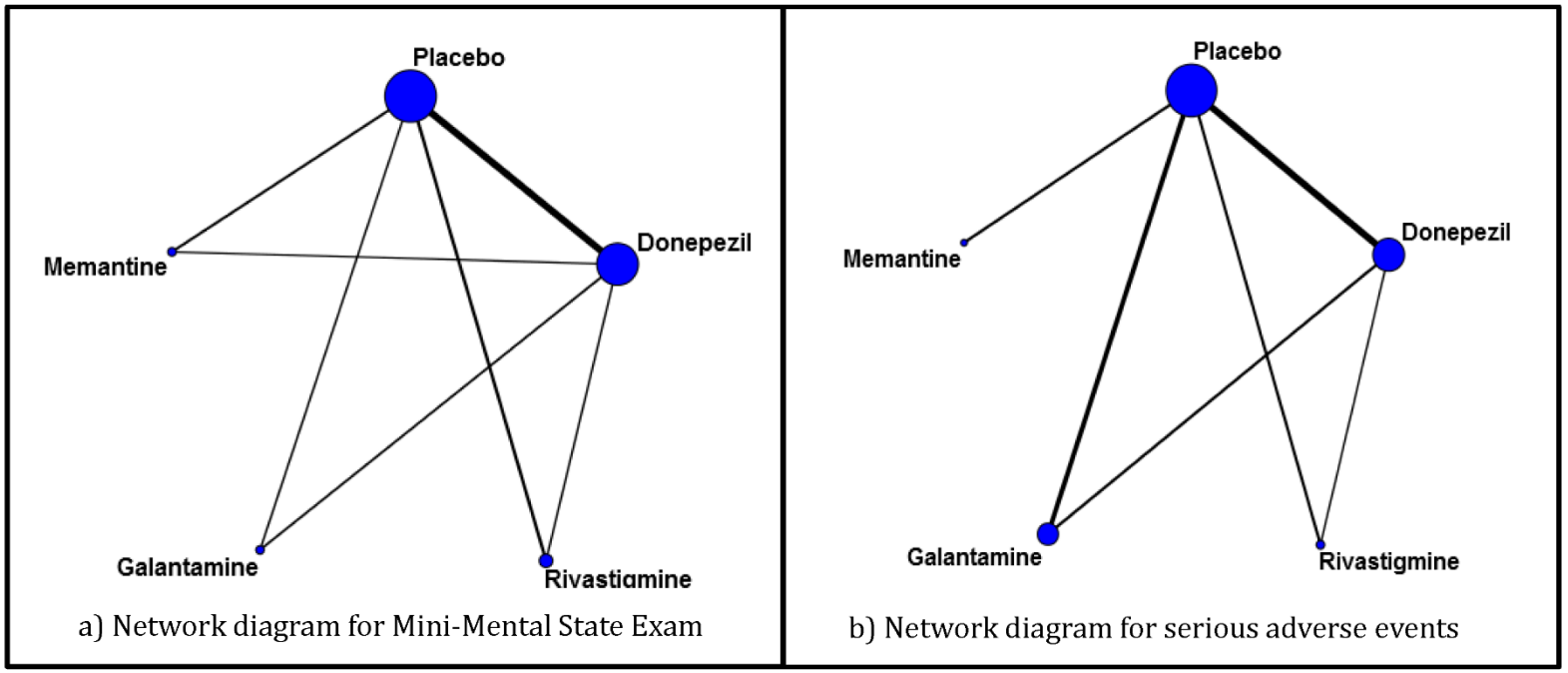
Aim

To update our previous systematic review and perform an IPD-NMA to evaluate the comparative safety and effectiveness of long- vs. intermediate-acting insulin in different subgroups of patients with T1DM

Network meta-analysis using IPD

Comparative safety and effectiveness of cognitive enhancers for Alzheimer's dementia

Tricco et al ODPRN 2015



a) Network diagram for Mini-Mental State Exam

b) Network diagram for serious adverse events

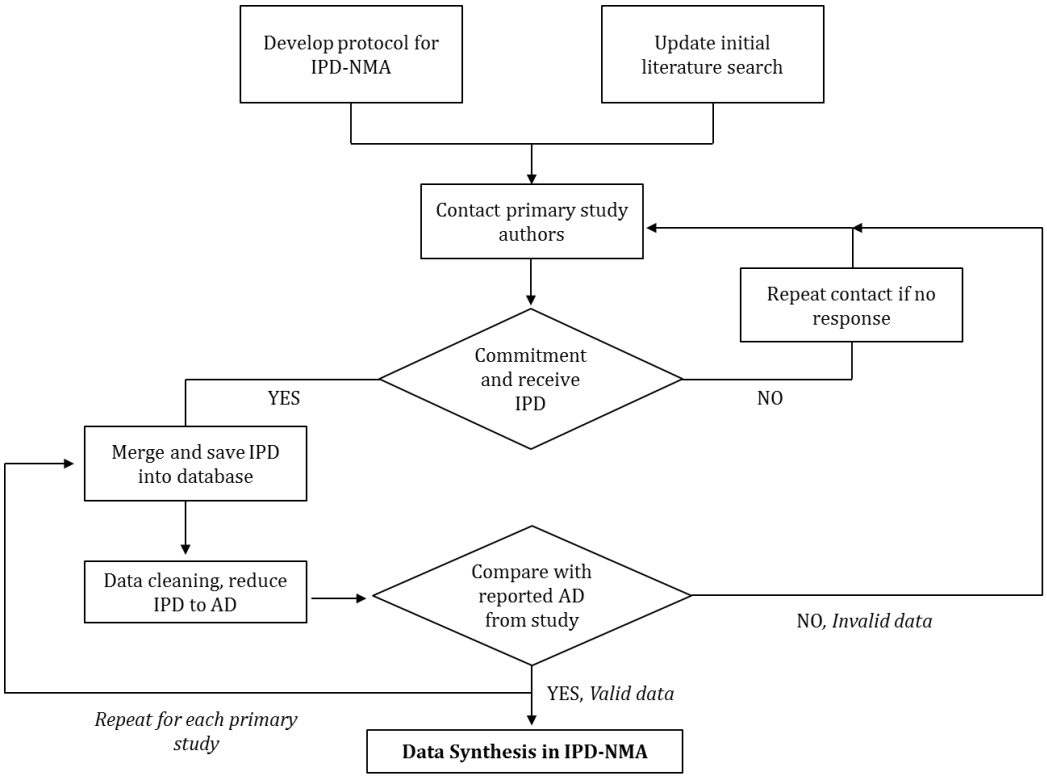
Veroniki et al BMJ Open 2016;6:1 e010251

Aim

To update our previous systematic review and perform an IPD-NMA to examine the comparative effectiveness and safety of cognitive enhancers for different patient characteristics

Process for an IPD-NMA

- Eligible trials identified by search as in an AD review
- Identify contact information for authors published each eligible study



- Response to request may vary (e.g., no reply, no with reason provided, yes - will send the data, yes – here are the data)
- Data format and supporting material can vary per IPD received

How to obtain IPD

Veroniki *et al. Trials* (2016) 17:138
DOI 10.1186/s13063-016-1238-z

Trials

STUDY PROTOCOL Open Access

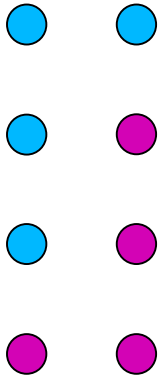
Contacting authors to retrieve individual patient data: study protocol for a randomized controlled trial

Areti Angeliki Veroniki[1], Sharon E. Straus[1,2], Huda Ashoor[1], Lesley A. Stewart[3], Mike Clarke[4] and Andrea C. Tricco[1,5*]

Aim

To examine the impact of providing incentives to the researchers responsible for the trials eligible for an NMA to submit their IPD

RCT Authors



Intervention Group

Control Group

Studies Within a Trial (SWAT) and Studies Within a Review (SWAR)
http://go.qub.ac.uk/SWAT-SWAR

How to obtain IPD

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Primary outcome:

Proportion of authors who provide complete IPD

Secondary outcomes:

1) Time taken to obtain the IPD between request and authors' provision
   - In case the authors send multiple datasets over a period of time, we will consider the last date of correspondence to estimate the time required to obtain IPD

2) Completeness of the IPD received (according to our requested info)
   - If an author provides us with the IPD and some variables are missing because these were not collected during the RCT, then this is a complete dataset

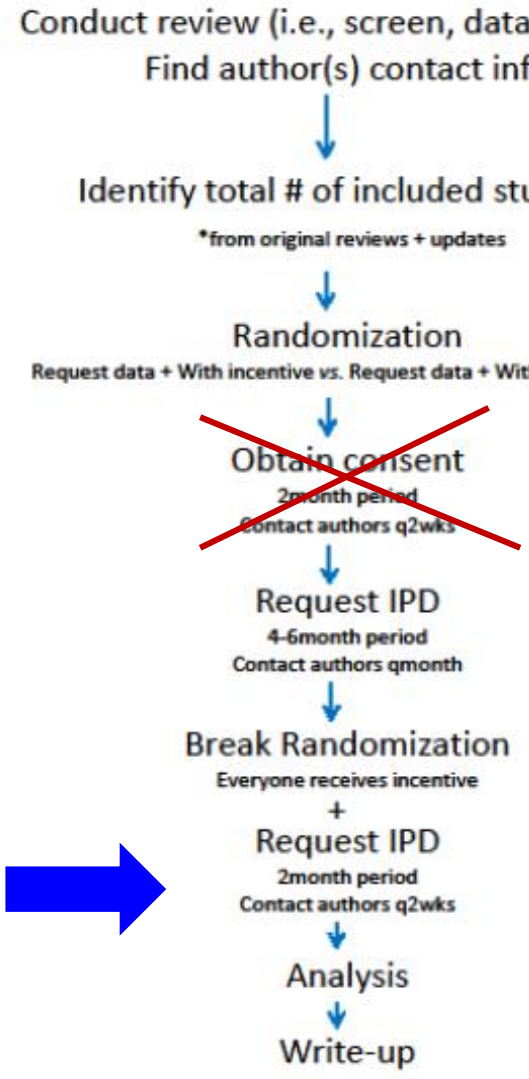
RCT Process

Update Systematic Reviews Phase

Data Acquisition Phase

Analysis Phase

Write-up of SR & IPD-NMA Phase



- After discussions with the REB, we decided to skip the participant consent step as it would bias our study results

Data requested on:

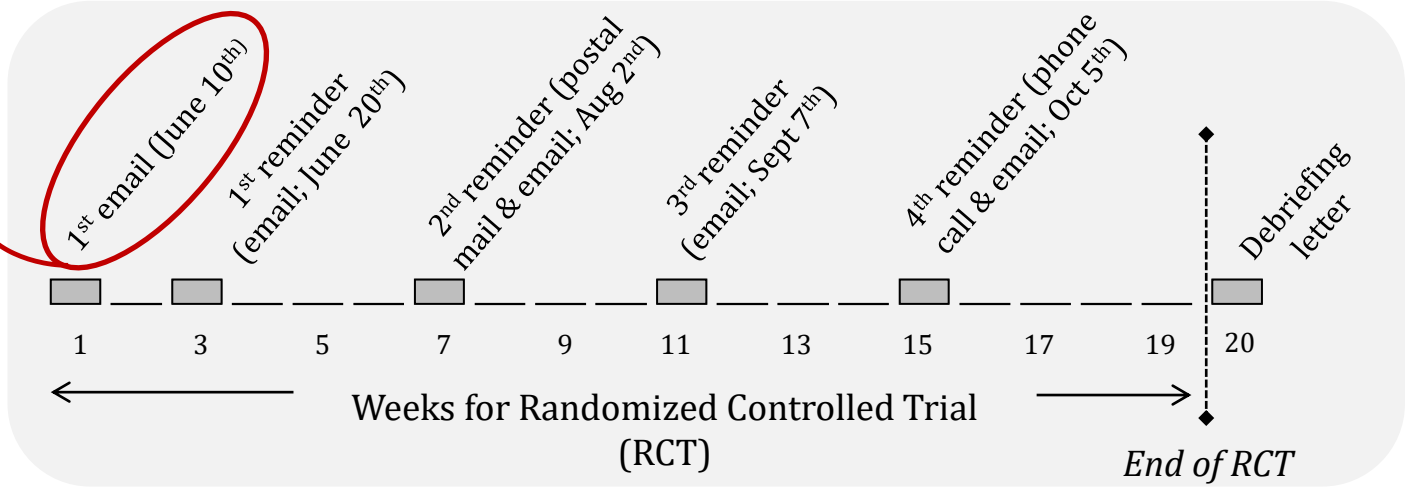
- Population (e.g., age, sex, pregnancy, presence of comorbid conditions)
- Interventions (e.g., allocated treatment, dosage)
- Outcomes (e.g. event and date of event)
- Date of randomization for each participant and overall method of randomization for all study participants

Steps to request for IPD from authors

Choice of authors (no duplicates allowed – no author was contacted more than once for each study during the RCT process):

- Corresponding authors
- If a corresponding author comes up for more than one study, the next available author was used (first author, if not corresponding)
  - This step was repeated if the first author also appears more than once (move onto second author, third author, etc)
- Final list of authors to be contacted did not have any duplicates
- If in the event an email is undeliverable, we searched for an alternative email. If none was to be found, the next available author was contacted

specify data we are requesting, provide summary/protocol of our study



** Some dates vary because many emails bounced on the first try. But this is the general timeline*

Cases we encountered during the RCT process

The primary author who was contacted:

1. Does not have the IPD, but facilitates the process of us getting the IPD from somebody else (e.g., sponsor, corresponding author)
2. Does not have the IPD, but re-directs us to a corresponding author that has already been contacted for another study
3. Does not have the IPD, but instead has contacted another person on our behalf
4. Does not have the IPD and is not willing to help, and does not refer us to an author/sponsor
5. Has the IPD but does not have the time to retrieve and send the data to us
6. Does not have a working email address for the initial invite
7. Has an out-of-office reply

Negative responses	**Positive responses**
E.g., Contact funder/database, lack of resources/time, do not have approval/ownership, do not have data, old data, not interested, contact corresponding author	E.g., contact corresponding author/funder – provided contact person, interested, contacted funder

Steps to request for IPD from sponsors

Initial inquiry phase

General email/phone inquiry sent to all sponsors to achieve the following:

- Confirm what their process is, and ask if there are any 'special' steps we need to be aware of
- Ask whether they are able to provide their signatory and contact info of their 'point-person' to facilitate our data sharing agreements (DSA)
- Ask if the DSA is available in WORD format, in case we need to make any changes
- A maximum of two follow-up emails/calls were sent if there was no response within 2 weeks.

Preparing research proposals

<u>All sponsors require the following:</u>

1. Research application/proposal
2. Statistical analysis plan (SAP), including Clinical Trials requested and Publication Plan
3. Data sharing agreement
4. Conflict of Interests for primary investigators

<u>Some require the additional steps:</u>

5. Provide with CV's of PI and team requesting data
6. Data and information privacy agreement – Abbvie

Co-sponsored studies were identified

We contacted all sponsors listed in the publication to increase our chances to obtain the IPD

Steps to request for IPD from sponsors

Statistical Analysis Plan General Requirements

- Description of the population to be analyzed
- Inclusion/exclusion criteria
- A description of the endpoints and time points to be analyzed
- Effect measure of interest (e.g. risk ratio, risk difference, absolute difference, rate with CIs)
- Any transformation of data
- Statistical models, including the statistical approach (e.g. Bayesian or frequentist), meta-analysis approach (e.g. random-effects model, stratified meta-analysis), and tests (e.g. Fisher's exact test, Kaplan-Meier curves, log-rank test to compare groups, multiplicity adjustments)
- Model fit tests, sensitivity or heterogeneity analyses (e.g. Chi-Squared Test, I squared statistic)
- Methods to control for bias – assumptions and any planned adjustments for covariates or meta-regression or modelling of covariates or subgroup analyses (e.g. by age, disease status, ethnicity, socioeconomic status, presence or absence or co-morbidities, by drug dose)
- Statistical power calculations or the precision of the effect estimate given the sample size available, and levels of significance
- Handling of missing data
- The strengths and limitations of the research
- How the results are going to be presented

Steps to request for IPD from sponsors

Legal processes and issues involved in accessing IPD

- While the process varies depending on the institution, it is generally becoming more complex due to the increasing use of Data Sharing Agreements
- Individual investigators based at an institution are usually not allowed to sign the agreement on behalf of the institution
- Liaise with legal teams in academic institutions and pharmaceutical companies to ensure that the resulting agreements protect both those providing the IPD and the data requester
- Institutions are also often faced with unfamiliar wording (e.g. from different countries)
- Variety of detailed amendments to clauses may be required (e.g., only being able to operate under the Canadian laws)
- Definition of what the intellectual property (IP) rights are going to be
- Requesting additional protection on data systems
- Issues may be raised regarding accessing data if there was no explicit mention in the patient's original consent that the data could be transferred –depends on REB approval

Steps to request for IPD from sponsors

Research Contracts

- Our contracts team reviews contracts and liaises with the sponsors (external party) to annotate/revise the terms and conditions
- Our contracts team meets (when necessary) with our research team to discuss any issues that arise during the review of contracts
- The Intellectual Property (IP) section is usually slightly re-worded by both parties, which can lead to extra delays
- One of the reasons that IP clauses often present a problem is that there can be doubts and debate about who owns the processed data
    - For example, if a gene array belonging to a patient is provided to the researcher then the blood sample may belong to the patient, **but** if a complex analysis has been run against that sample, it is not always clear who owns the results of that
- **Cochrane IPD Meta-analysis Group** suggests encouraging trialists to ask patients to agree to share their data openly with other research teams when their consent is sought
    - if the level of consent varies between patients in a trial, then this may lead to even less data becoming available

Cochrane Methods
IPD Meta-analysis

Steps to request for IPD from sponsors

Research Contracts

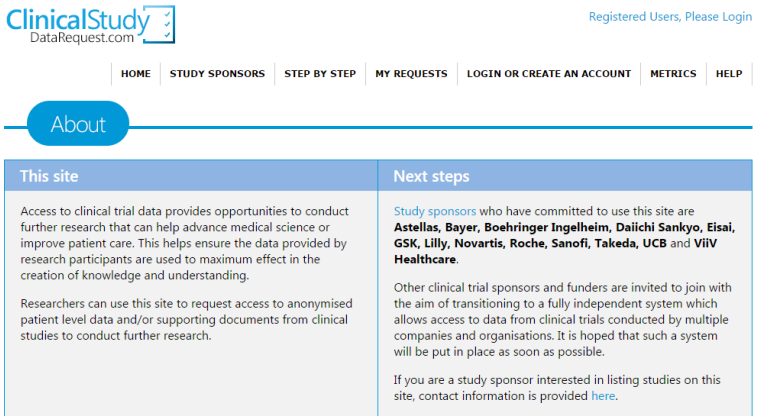
- When a DSA has been reviewed by the contracts team, they are sent to the director of the Knowledge Translation Program (KTP; Dr. Sharon E. Straus) and to Vice President, Research (Dr. Arthur Slutsky) for review
- Terms and Conditions: Most research contracts require the researcher to provide the company copies of the material the researcher intends to present/publish well ahead (e.g., 45 days) prior to submission in order to allow the company to review it.
    - "*If Company determines, in its discretion, that Company Confidential Information is intended to be disclosed, it may require Researcher to redact the Company Confidential Information. Researcher agrees to consider all other comments of Company in good faith.*"
- After review, the DSA is signed by the project team members, the director of the KTP, and VP Research
- Submissions are done via an online portal or direct email

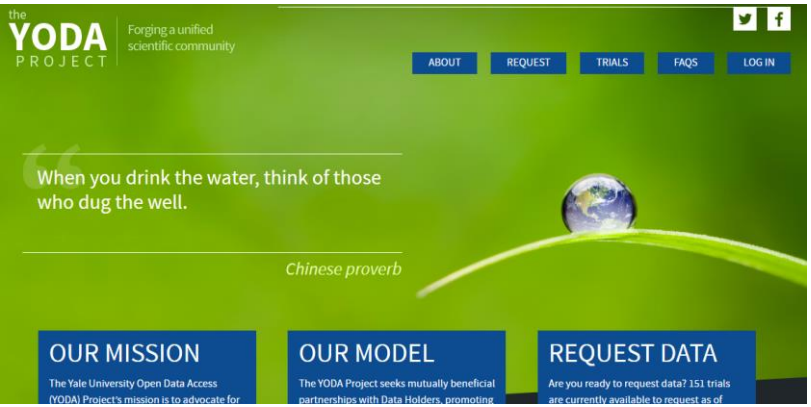
How long will it take to obtain the IPD after submission?

- It can take up to 1 year to process and reject/accept the proposal
- Many sponsors do not specify how often they will be in contact with us for an application in process

IPD databases

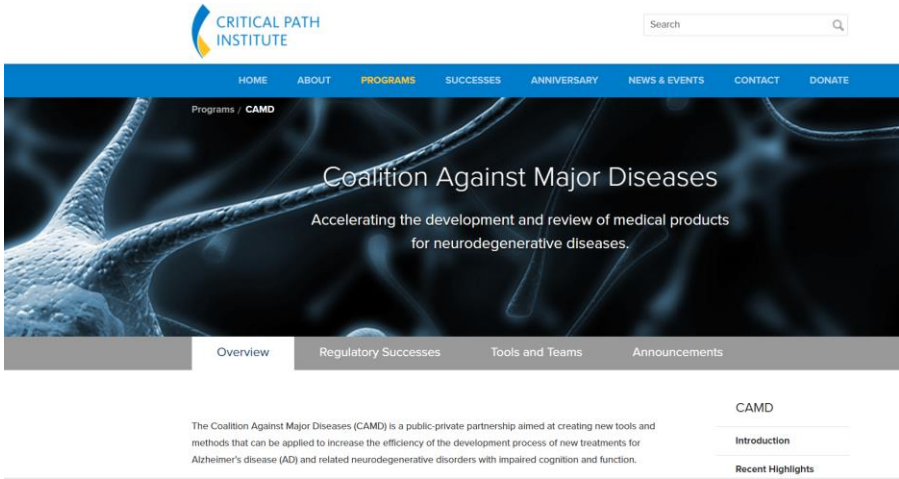
The Clinical Study Data Request (CSDR) System:
https://www.clinicalstudydatarequest.com/





The Yale University Open Data Access (YODA) Project:
http://yoda.yale.edu/

The Coalition Against Major Diseases (CAMD):
https://c-path.org/programs/camd/



Steps to request for IPD from IPD databases

Initial inquiry phase

General email/phone inquiry sent to all sponsors and databases to achieve the following:

- Confirm what their process is, and ask if there are any 'special' steps we need to be aware of
- Ask whether they are able to provide their signatory and contact info of their 'point-person' to facilitate our data sharing agreements (DSA)
- Ask if the DSA is available in WORD format, in case we need to make any changes
- Two follow-up emails/calls were sent if there was no response within 2 weeks

Inquiring for availability of studies

- Prior to submitting a research proposal, we were required to inquire for the availability of the studies in each database
- A list of studies for each sponsor within the database was provided to inquire for availability
- For studies ***not included*** in the Trial List, we contacted both IPD database and sponsor
- Once the sponsor confirms which of the studies are available in the database, the application to request for IPD can start
    - Note, at this stage, we reached a *dead end* for some studies since the sponsor deemed them as *"Not Available"* – these studies were excluded from our application

Steps to request for IPD from IPD databases

- The preparation of research proposals and research contracts require the same exact steps as in the process of requesting IPD from sponsors
- Some databases require an upfront Data Use Agreement (DUA) (e.g., YODA)

- The YODA DUA requests:
  - No distribution of the data to third parties or public posting of the data is permitted – protect the confidentiality of the data

Important consideration:
protect the privacy and confidentiality of research participants
(anonymised data sharing)

  - All results must be reported to the YODA Project at the time of DUA expiration or upon completion of the research project
  - Any public dissemination of the findings resulting from the proposed research will be required to take place through peer-reviewed publication
  - All public dissemination of the findings will be required to mention that the analyses were based on data made available via the Yale University Open Data Access Project

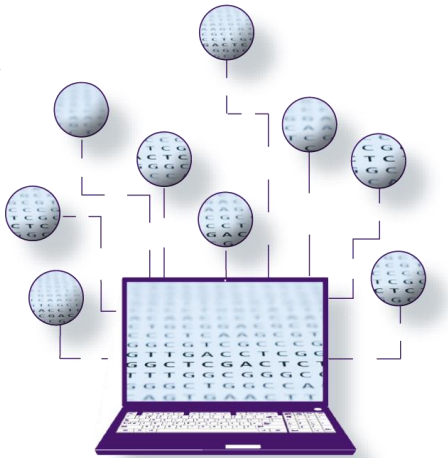
- CSDR IPD database requires: For >1 inquiries ongoing with several sponsors a ***single*** proposal should be submitted including all studies – once the individual sponsors response positively to the inquiries

Steps to request for IPD from IPD databases

- **Purpose of review process**
  1. Ensure that the research proposal has scientific merit
  2. The scientific purpose is clearly described
  3. The data requested will be used to create or materially enhance generalizable scientific and/or medical knowledge to inform science and public health
  4. The proposed research can be reasonably addressed using the requested data

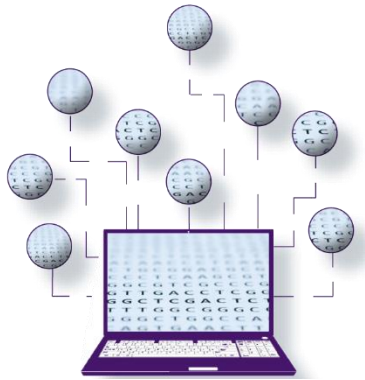
- One of the criticisms of the IPD approach is that it can take quite a long time to access the data, even via platforms such as YODA or CSDR

- Cochrane IPDMG members experience shows that
  - It takes about 1 year to obtain IPD
  - Two-stage analysis can only be applied as we can access IPD through their suggested channels
  - Challenges encountered include using unfamiliar software and negotiating with numerous firewalls
  - Delays when having to withdraw the original request to "add" additional trials not available at that time



Data sharing experiences for an updated NMA

- IPD for 39 trials (8,261 participants) were requested from the CSDR database and the relevant sponsors, between June 2013 and December 2015
- First/corresponding authors and trial sponsors were contacted by email, post and fax
- IPD were received for 15 (38%) trials [5,335 (65%) participants]
  - Total number of IPD provided for NMA: 10,038 (71%) of 14,148 participants from 33 (49%) of 68 studies
- Time from initial request to receiving a response: median 343 (range: 17-725) days
- Time taken to receive IPD for one trial using CSDR 364 days
- Failed to retrieve IPD from 24 (62%) trials (published between 1989 and 2012)
- 11 trials provided reasons for negative response (time from initial request to response median 287 (range: 0-764) days):
  - Restrictions specific to a country over anonymization of data
  - Cost of retrieving and preparing data
  - Concerns about ethical approval for sharing data
  - Requested data had not been recorded
  - Data were lost
- The remaining 13 trials (median 972 (range: 640-1448) days):
  - 2 responded initially positively, but data were never provided
  - 11 gave no response



Nevitt et al BMJ 2017

Process when IPD are obtained…

Sponsors and IPD databases

- Provide data in a secure environment
  - Researchers are provided with access to anonymized data in a secure environment in which they conduct their analysis. Protections are in place to prevent the removal of raw data

When IPD are provided inside/outside secure environments:

- Understand the data (check the protocol and decipher the variable codes)
- Reproduce published results
- Check the data (e.g., missing participants, chronological randomization sequence)
- Raise queries and discuss them with original authors/sponsors/IPD databases
- Clean and prepare data in a common format across all studies
  - Recode data to a consistent format
- Define outcomes of interest consistently across trials
- Perform analysis of the data
- Share results with data providers for discussion (if needed)
- Report findings according to the Preferred Reporting Items for a Systematic Review and Meta-analysis of Individual Participant Data (PRISMA-IPD) guidelines

Stewart et al JAMA 2015

Contacting authors/sponsors & databases to obtain IPD

- Initially, 140 authors were to be contacted between June 10, 2016 and November 16, 2016
  - However, we were unable to locate a valid email contact for any and all authors for 4 studies - those studies were removed
  - One study was unpublished report – and was removed from the sample
- In total, we contacted 135 authors
  - Each author was contacted for a single RCT
  - To date, 38% of authors did not respond
- We have 12 research applications in progress to be submitted to the relevant sponsors/databases
  - 4 of them required an upfront DSA
  - 7 research application were submitted
- 5 DSAs are in progress
- 4 sponsors did not respond
- 4 sponsors cannot share data

In summary....

Why conduct an IPD-(network) meta-analysis?

- Individual study results do not answer all potentially relevant clinical questions
  - Previous NMAs based on AD may have limitations
- Enables further research to benefit medical research and patient care
- Enables tailoring results to patient characteristics, and hence improving existing guideline recommendations
- Enables the validation of individual study results
- Helps avoid duplication of research, unnecessarily enrolling patients into clinical trials and exposing them to possible risks (e.g., serious adverse events)
- Increases transparency

But...

- If the clinical trial community continues to fail with respect to data sharing, we will only strengthen the public perception that we do clinical trials to benefit ourselves, not patients
- Conclusions of IPD meta-analyses are vulnerable to distortion when trial sponsors have strong interests that might benefit from promoting selected data
- Further studies are needed to evaluate the assumptions and the properties of an IPD-NMA in complex networks of interventions

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For details on our work please visit http://knowledgetranslation.net/

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