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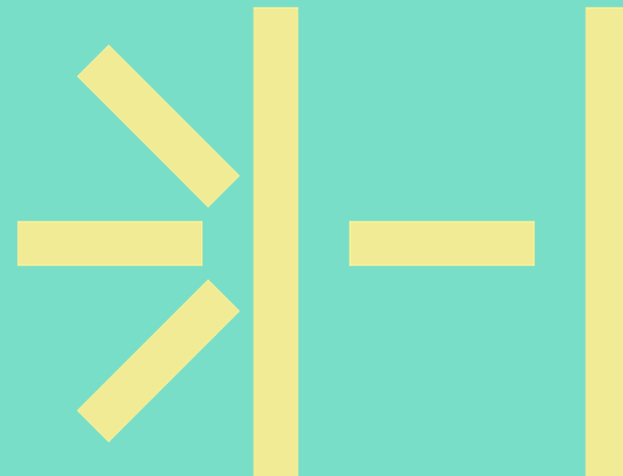


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Meta-research to improve evidence generation and synthesis

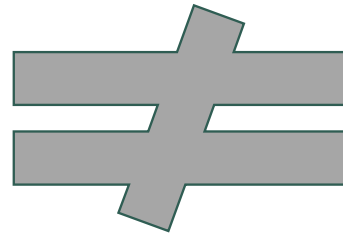
Prof. Matthias Briel MD PhD

CLEAR-Methods Center, Division of Clinical Epidemiology, Department of Clinical Research,
University Hospital Basel, Switzerland



The STRATOS initiative

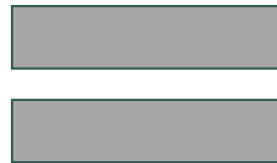
*STR*engthening *AN*alytical *TH*inking for *OB*servational *ST*udies



Randomized clinical trials (RCTs)
Individual Participant Data Meta-Analysis (IPDMA)

The STRATOS initiative

*STR*engthening *AN*alytical *TH*inking for *OB*servational *ST*udies



Meta-research on
Randomized clinical trials (RCTs)
Individual Participant Data Meta-Analysis (IPDMA)

Randomized clinical trials (RCTs)

- High quality RCTs are challenging and resource-demanding
- RCTs are often not conducted as initially planned
- RCTs are at risk to be discontinued for different reasons:
 - Harm
 - Early superiority
 - Futility
 - Running out of funding
 - Strategic reason by sponsor
 - Insufficient recruitment
- **Ethical issues with discontinued RCTs** (dissemination, information of ethics committees & participants, resource waste)

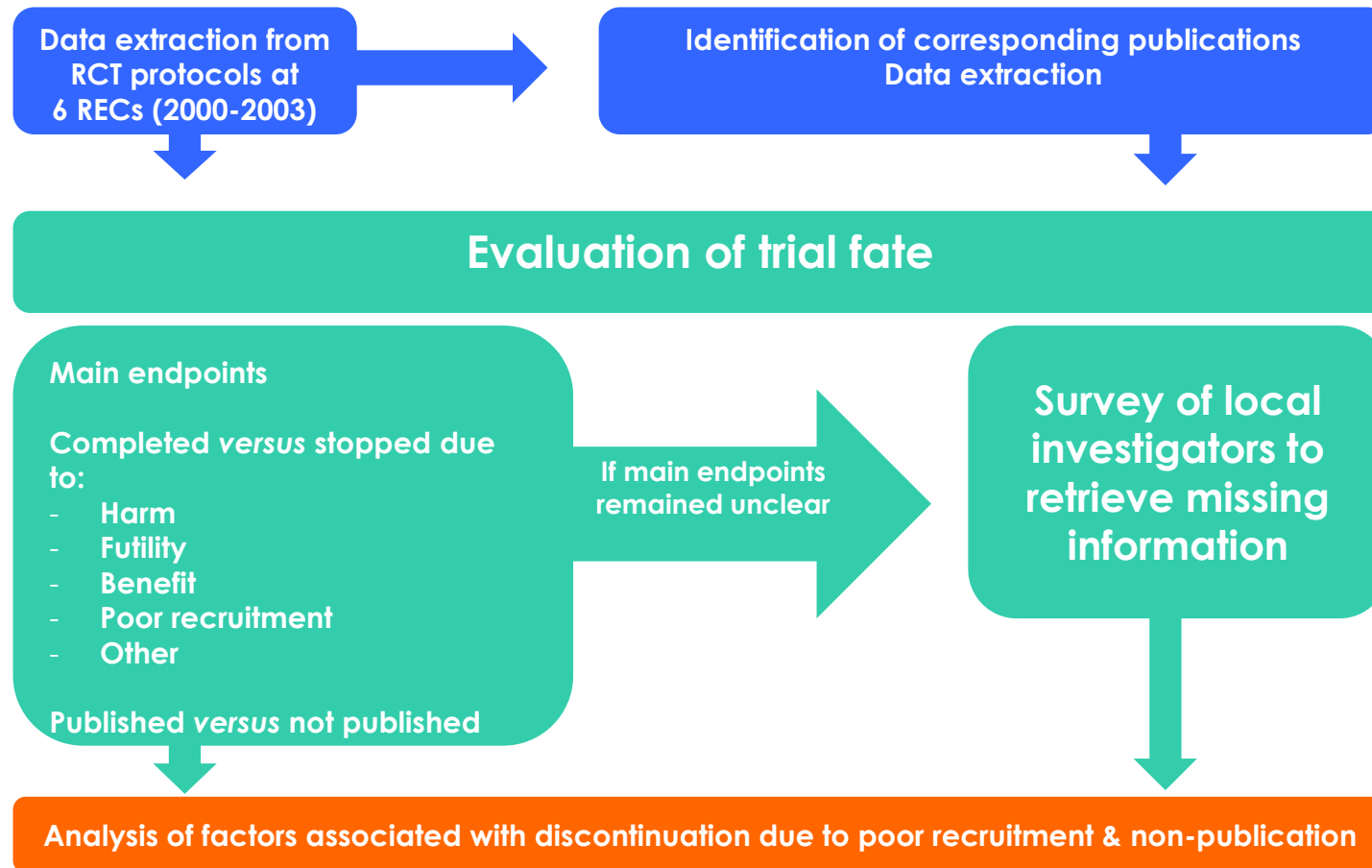
Epidemiology and publication history of discontinued RCTs unclear

How often are RCTs discontinued?

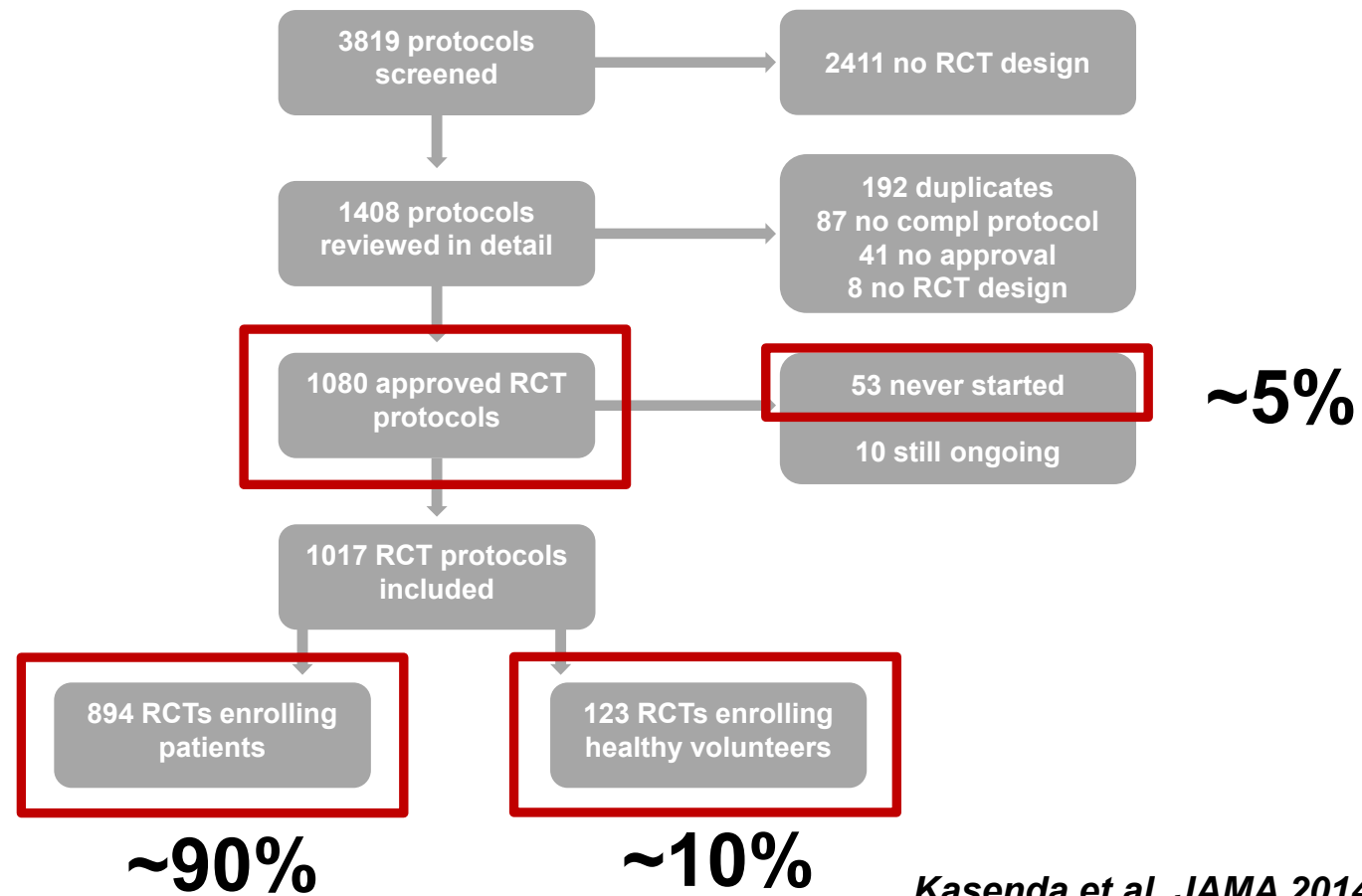
Reasons for discontinuation?

How often are RCT results available?

DISCOntinued Trials Study (DISCO I)

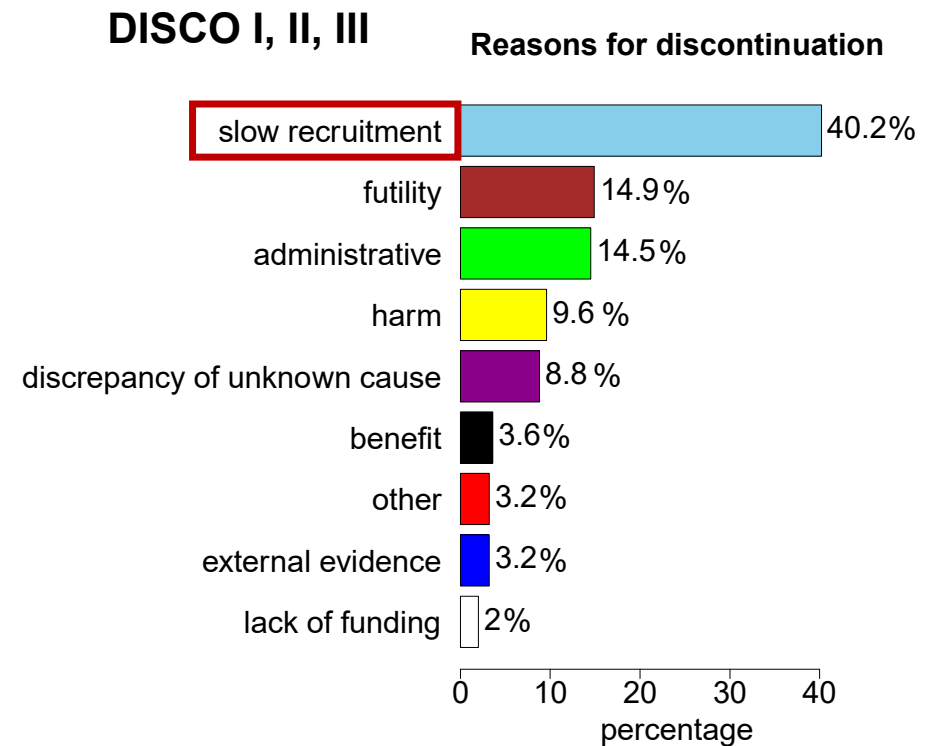
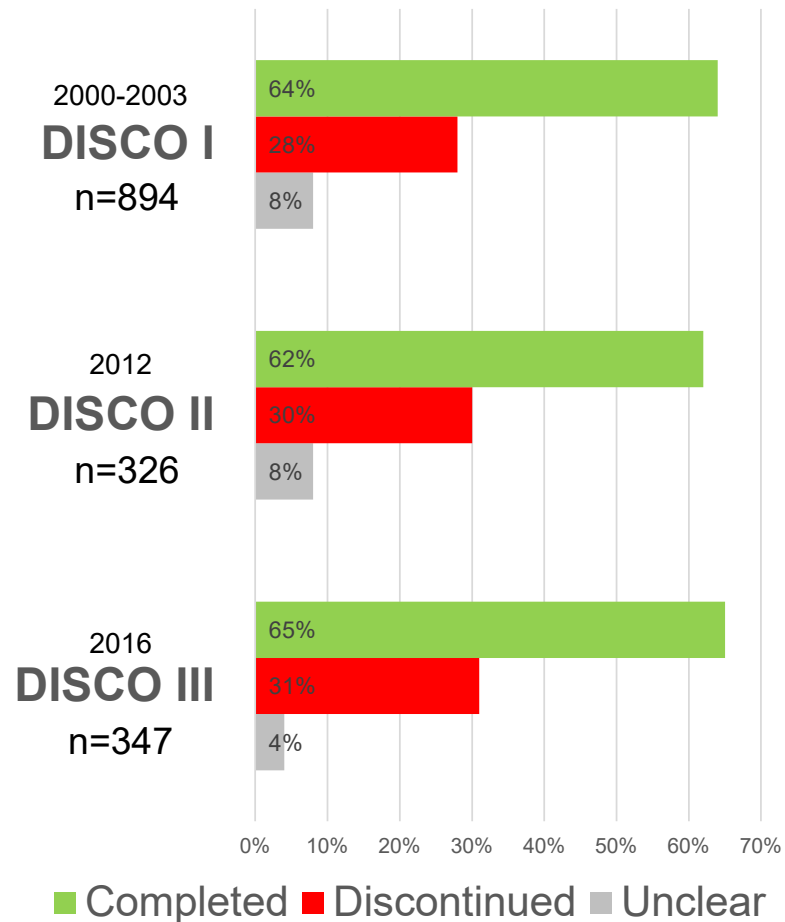


DISCO I – Study Sample



Kasenda et al. JAMA 2014

Trial Discontinuation – DISCO I, II, and III



Risk Factors for Discontinuation including Acute Care & Peds

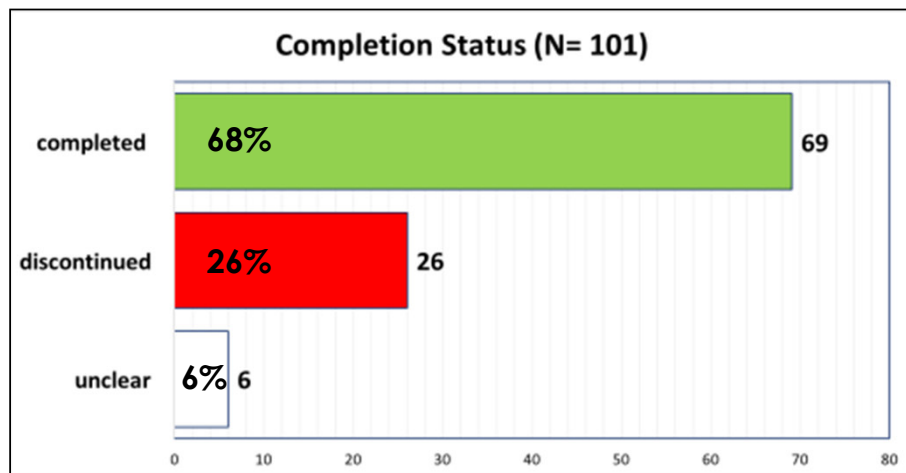
Characteristics	OR	95% CI	P-value
Planned target sample size (steps of 100)	0.96	0.92 – 1.00	0.042
Placebo/no-active control (vs active control intervention)	0.81	0.50 - 1.31	0.387
Single centre status (vs multi-centre)	0.66	0.32 - 1.38	0.274
Cross-over design (vs parallel)	2.00	0.75 – 5.33	0.163
Reported methodological/logistical support (vs not reported)	0.62	0.37 - 1.06	0.083
Reported recruitment projection (vs not reported)	1.04	0.50 - 2.22	0.900
Industry sponsor (vs investigator)	0.25	0.15 - 0.43	<0.001
Acute care RCT (vs nonacute care)	4.00	1.72 – 9.31	0.002
Pediatric RCT (vs adult)	1.22	0.57 – 2.63	0.610

Schandelmaier et al. Crit Care Med 2015
Kasenda et al. JAMA 2014

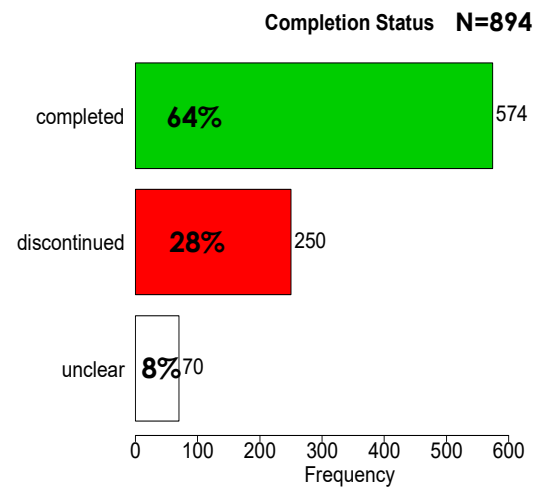
RCTs supported by the Swiss National Science Foundation (SNSF) from 1986-2015

Discontinuation of SNSF-supported RCTs

SNSF Study



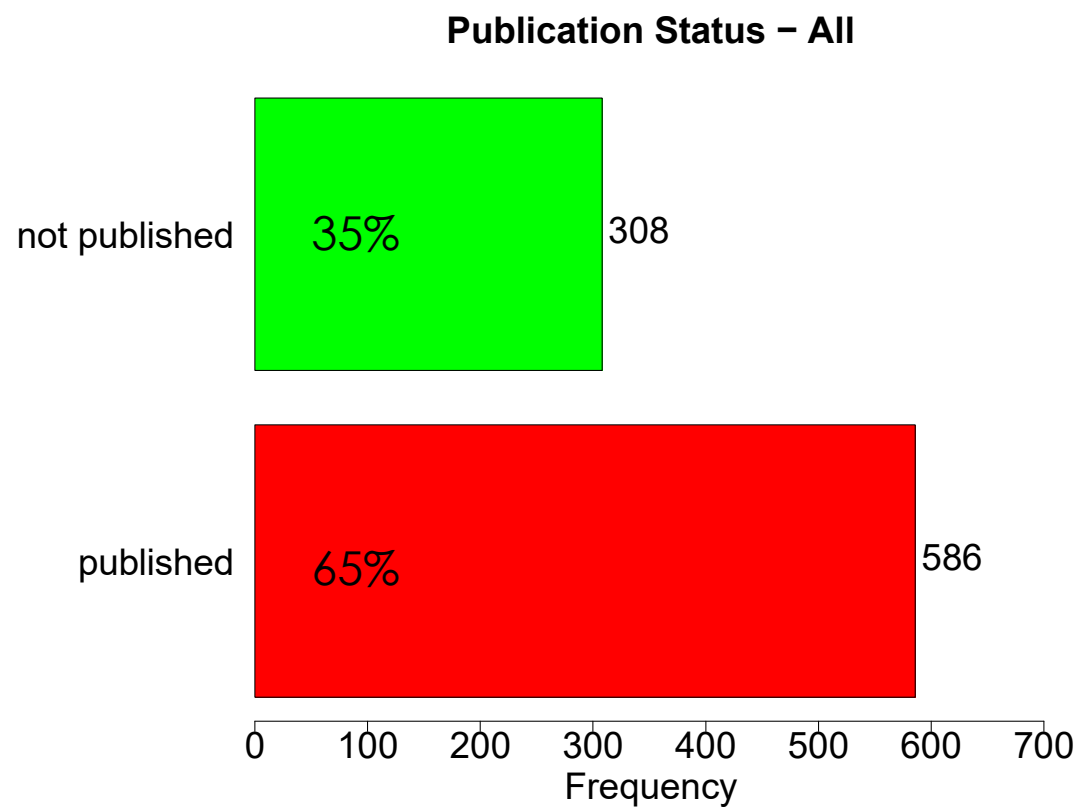
DISCO I Study



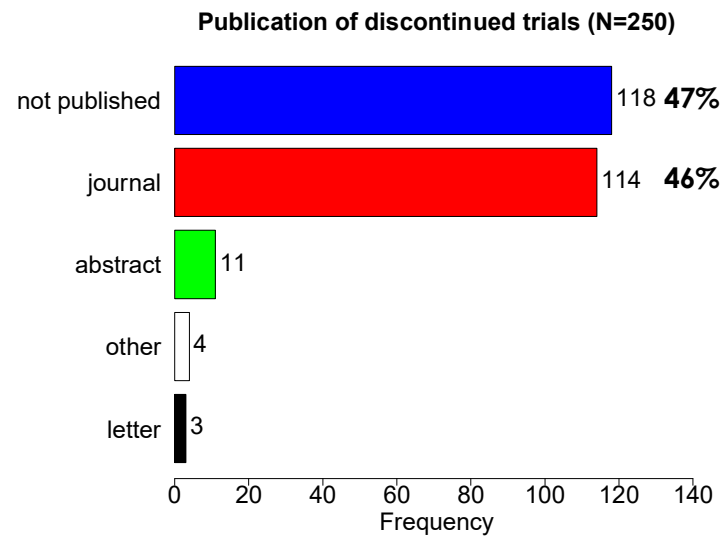
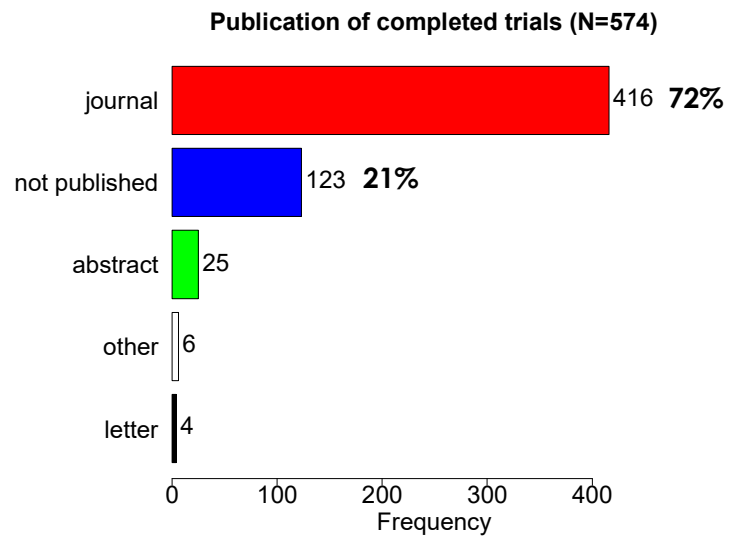
Reason for premature discontinuation:
All due to slow recruitment !!!

Amstutz et al. BMJ open 2017

Results DISCO I: Trial Publications



Results DISCO I: Trial Publications



Kasenda et al. JAMA 2014;311:1045-1051

Results DISCO I: Risk Factors for Non-Publication

Characteristics	OR	95% CI	P-value
Planned target sample size, median (IQR)	0.95	0.92 - 0.97	<0.001
Multi-centre status (vs single centre)	0.50	0.32 - 0.76	0.001
Industry sponsor (vs investigator)	1.68	1.20 - 2.34	0.002
Discontinued RCT (vs completed RCT)	3.19	2.29 - 4.43	<0.001
RCT with patients (vs healthy volunteers)	0.36	0.20 - 0.63	<0.001

Kasenda et al. JAMA 2014;311:1045-1051

DISCO II & III – Trial results availability

All RCTs



	All RCTs approved in 2012 (n=326)	All RCTs approved in 2016 (n=347)
Results availability		
At any source (peer-reviewed publication or on trial registry)	261 (80.1%)	276 (79.5%)
Peer reviewed publication	248 (76.1%)	249 (71.8%)
In trial registry	168 (51.5%)	170 (49.0%)
Results not available (neither publication nor trial registry)	65 (19.9%)	71 (20.5%)

DISCO II & III – Trial results availability

Industry vs. non-industry RCTs

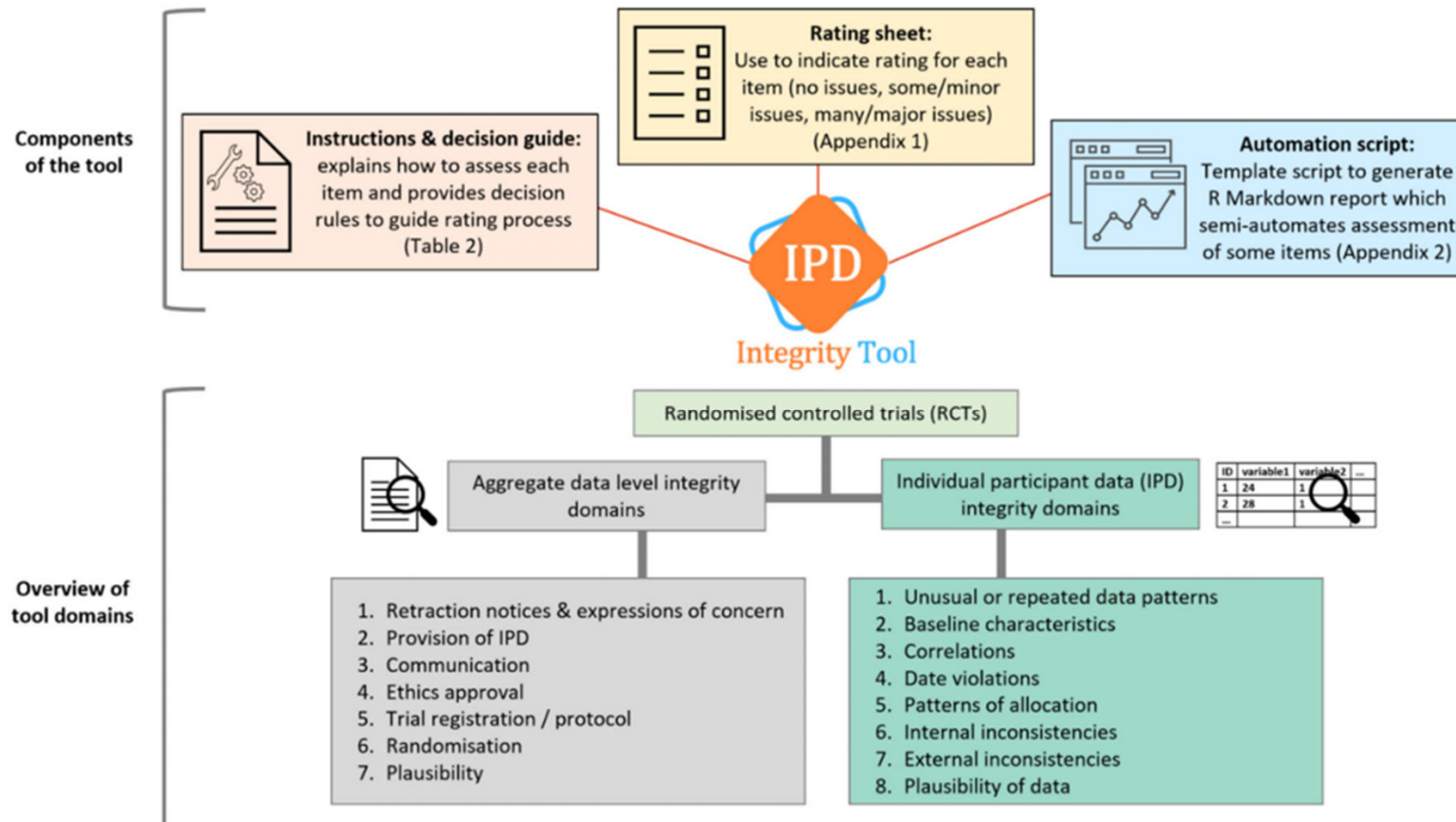
	2012			2016		
	Industry sponsored RCTs (n=179)	Non-industry sponsored RCTs (n=147)	All RCTs (n=326)	Industry sponsored RCTs (n=181)	Non-industry sponsored RCTs (n=166)	All RCTs (n=347)
Results availability						
At any source (peer-reviewed publication or on trial registry)	172 (96.1%)	112 (76.2%)	284 (87.1%)	166 (91.7%)	110 (66.3%)	276 (79.5%)
Peer reviewed publication	146 (81.6%)	110 (74.8%)	256 (78.5%)	140 (77.4%)	109 (65.7%)	249 (71.8%)
In trial registry	150 (83.8%)	23 (15.7%)	173 (53.1%)	153 (84.5%)	17 (10.2%)	170 (49.0%)
Results not available (neither as publication nor in trial registry)	7 (3.9%)	35 (23.8%)	42 (12.9%)	15 (8.3%)	56 (33.7%)	71 (20.5%)

Evidence Synthesis for informed Decision-Making

“Body of evidence” compromised through...

- Non-publication of trial results (trial registers, sensitive search) -
- Higher probability for publication of “positive” results (publication bias) -
- Low methodological quality (high risk of bias) -
- Low reporting quality of trials (reporting guidelines – CONSORT) IPDMA helps
- Heterogeneity of trial outcomes (COMET) and subgroup definitions IPDMA helps
- Inappropriate/inefficient statistical methods IPDMA helps
- Retrospective study protocol & hypotheses prospective MA helps
- Low trustworthiness of trials (INSPECT-SR) IPDMA helps

IPD Integrity tool by Hunter et al. Res Syn Meth 2024



Own IPDMA Expertise

Citation	Journal	Medical field	Trials	Pats	Duration (months)
Briel et al. 2010	JAMA	Intensive care (PEEP in ARDS)	3	2299 (100%)	24
Schuetz et al. 2012	Clin Infect Dis	Infectious Dis (PCT test)	14	4221 (100%)	49
Briel et al. 2018	Clin Infect Dis	Infectious Dis (steroids in CAP)	6	1506 (100%)	63
Schunemann et al. 2020	Lancet Haematol	Oncology (heparin in cancer)	14/20	8'278 (79%)	78
Amstutz et al. 2023	Lancet Respir Med	COVID-19 (remdesivir)	8/9	10'480 (99%)	21
Amstutz et al. 2025	Lancet Respir Med	COVID-19 (JAK-inhibitors)	12/16	12'902 (96%)	20

Hands-on Expertise published

Ventresca et al. *BMC Medical Research Methodology* (2020) 20:113
<https://doi.org/10.1186/s12874-020-00964-6>

BMC Medical Research
Methodology

RESEARCH ARTICLE

Open Access

Most resource intense
& time consuming
steps

Obtaining and managing data sets for individual participant data meta-analysis: scoping review and practical guide



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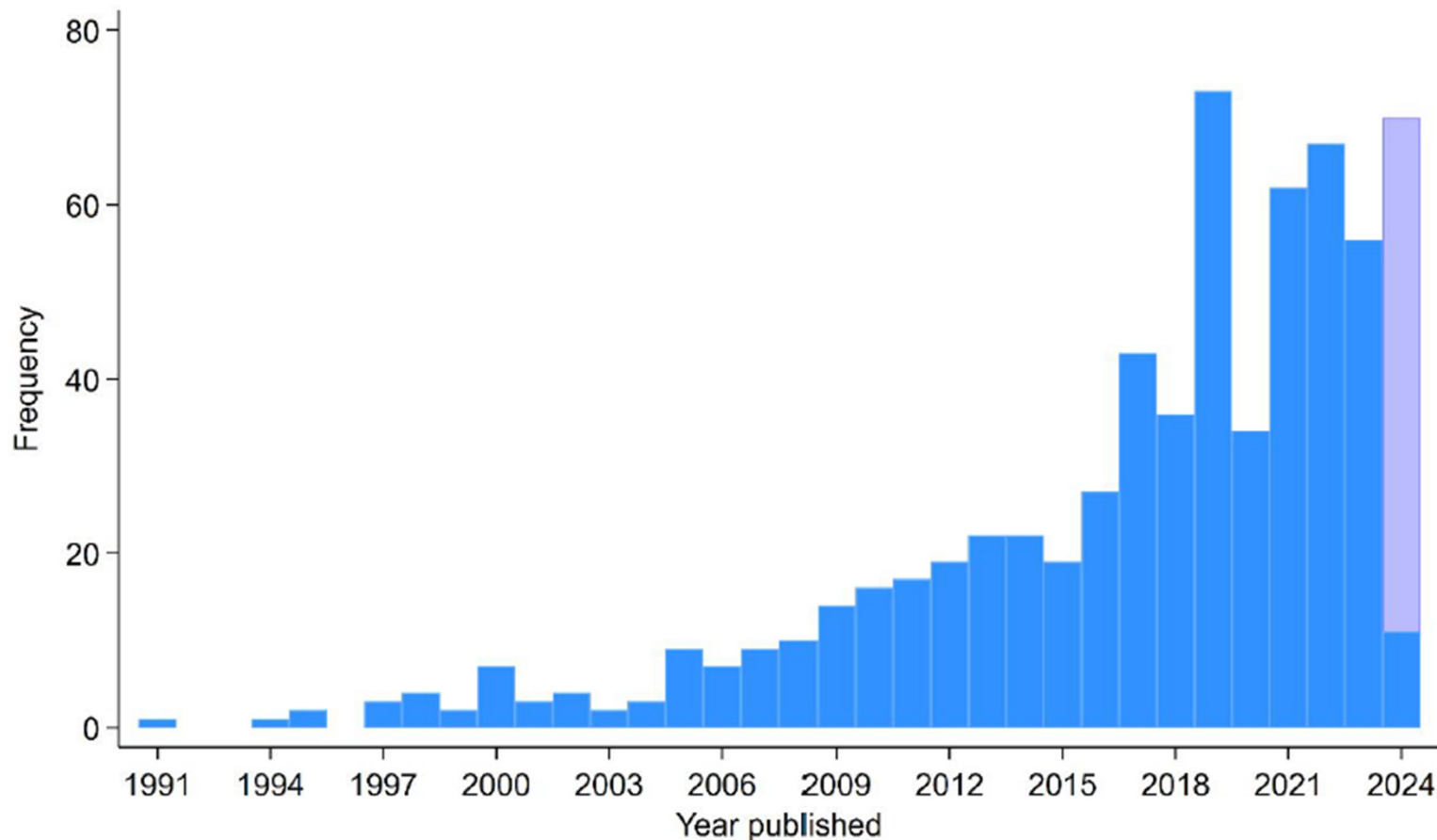
Abstract

Background: Shifts in data sharing policy have increased researchers' access to individual participant data (IPD) from clinical studies. Simultaneously the number of IPD meta-analyses (IPDMAs) is increasing. However, rates of data retrieval have not improved. Our goal was to describe the challenges of retrieving IPD for an IPDMA and provide practical guidance on obtaining and managing datasets based on a review of the literature and practical examples and observations.

Challenges of Optaining IPD

- Primary authors often lack time, funding, organisational resources for data sharing
- Some ask for financial support (100 - 2000 Euros) in addition to co-authorship
- Different rules/application forms for different data repositories (industry trials)
- Primary authors may agree to share IPD but never actually share IPD
- Decision to share often hinges on motivation of a single person
- Data sharing statement in publication may not prevent denial of IPD
- Small financial incentives (100 Can\$) not improved IPD retrieval (Veroniki et al. 2019, J Clin Epi)
- About 45% of IPDMAs obtain at least 80% of IPD (Nevitt et al. 2017, BMJ)
- only 60% of data sharing requests successful (Polanin JR 2018, J Clin Epi)
- To actually receive IPD after signing a data sharing agreement took between days and more than a year

«State of play» in IPDMA – Seidler & Godolphin



- N = 605 IPDMAs identified
- 1991 – 2024
- Mainly cardiovasc & cancer (20% each)
- Fewer IPDMA in Cochrane over time

«State of play» in IPDMA – Seidler & Godolphin

Sample of N = 100 IPDMAs from 2022 – 2024

Preliminary findings:

- Protocol available in 32%
- Statistical analysis plan available in 29%
- IPD obtained from investigators only 82%, repositories only 2%, both 7%
- Retrospective IPDMA in 87%, prospective IPDMA 13%

Prospective Meta-Analysis - FAME

PLOS MEDICINE

GUIDELINES AND GUIDANCE

A framework for prospective, adaptive meta-analysis (FAME) of aggregate data from randomised trials

Jayne F. Tierney¹*, David J. Fisher¹, Claire L. Vale, Sarah Burdett¹, Larysa H. Rydzewska¹, Ewelina Rogozińska¹, Peter J. Godolphin¹, Ian R. White¹, Mahesh K. B. Parmar¹

MRC Clinical Trials Unit at UCL, Institute of Clinical Trials & Methodology, University College London, United Kingdom

1. Start early, whilst trials are ongoing or yet to report

2. Liaise with trialists to get more info on trials

3. Predict earliest timing of reliable meta-analysis

4. Develop protocol and collect detailed data

5. Interpret meta-analysis taking account of available & unavailable data

Conclusions & Perspective

- **Trial discontinuation common & persistent**, esp. academic trials
- Most frequent reason: **poor participant recruitment**
- **Discontinued trials often not published**
- Discontinued trials should be **included in Meta-analysis**
- **IPDMA** has **many advantages** over aggregate MA, but **practically challenges**
- **IPDMAs** becoming **more frequent**, but **more transparency necessary**
- **Prospective MA** to further improve **evidence quality and trustworthiness**



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