The YODA Project:
A Use Case and Lessons Learned

Sharing Clinical Trial Data
NASEM Workshop
November 18, 2019

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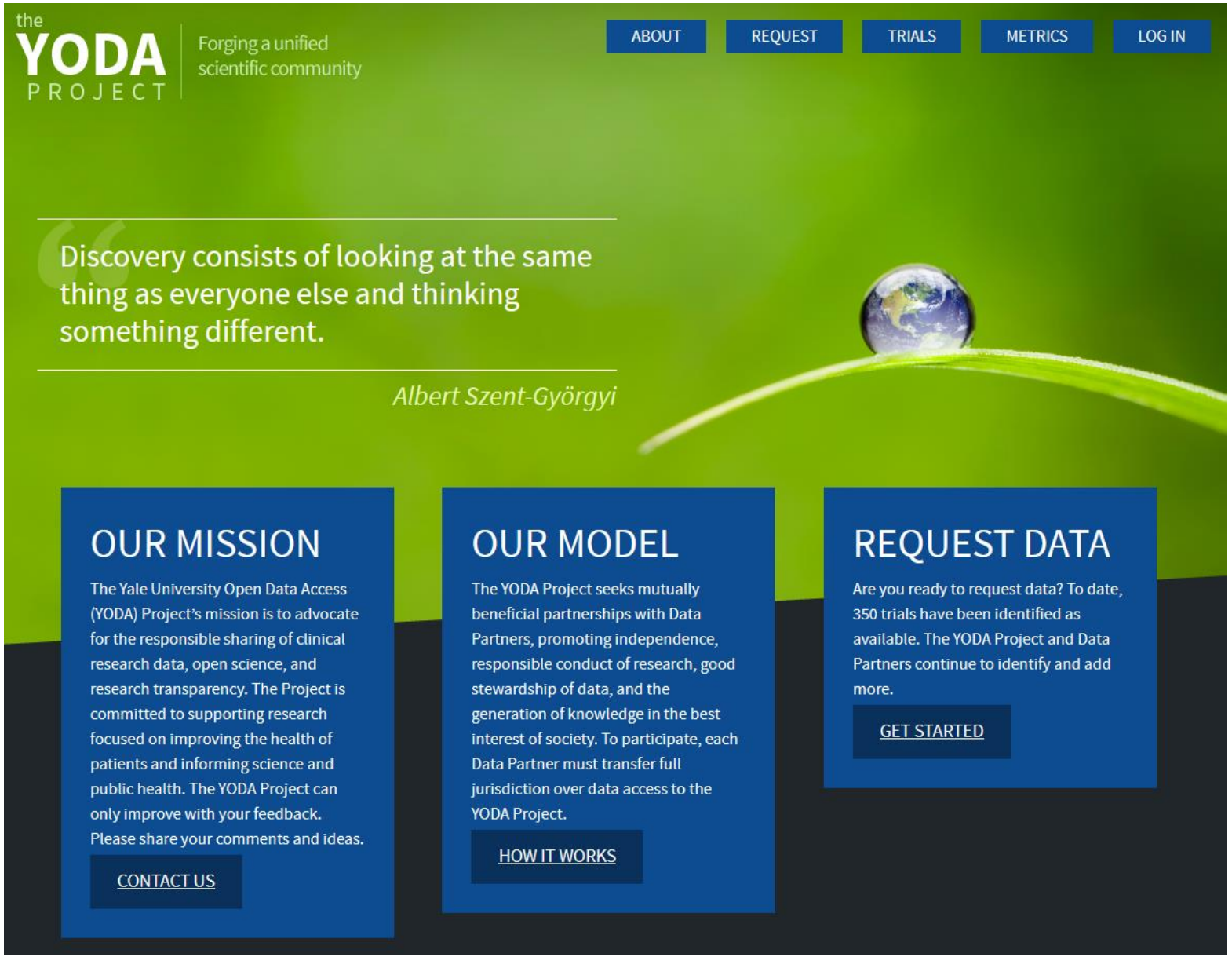
Potential Conflicts of Interest

- YODA Project funded by research grant through Yale from Johnson & Johnson, formerly funded by Medtronic, Inc.
- Research grant funding through Yale from:
  - Food and Drug Administration (FDA)
  - Centers for Medicare and Medicaid Services (CMS)
  - Blue Cross Blue Shield Association
  - NIH/NHLBI, AHRQ
  - Laura and John Arnold Foundation



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www.nature.com/scientificdata

SCIENTIFIC DATA

OPEN

Overview and experience of the YODA Project with clinical trial data sharing after 5 years

Joseph S. Ross[1,2,3,4], Joanne Waldstreicher[5], Stephen Bamford[6], Jesse A. Berlin[5], Karla Childers[5], Nihar R. Desai[4,7], Ginger Gamble[4], Cary P. Gross[1,2,4,8], Richard Kuntz[9], Richard Lehman[10], Peter Lins[5], Sandra A. Morris[5], Jessica D. Ritchie[4] & Harlan M. Krumholz[2,3,4,7]

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The Yale University Open Data Access (YODA) Project has facilitated access to clinical trial data since 2013. The purpose of this article is to provide an overview of the Project, describe key decisions that were made when establishing data sharing policies, and suggest how our experience and the experiences of our first two data generator partners, Medtronic, Inc. and Johnson & Johnson, can be used to enhance other ongoing or future initiatives.

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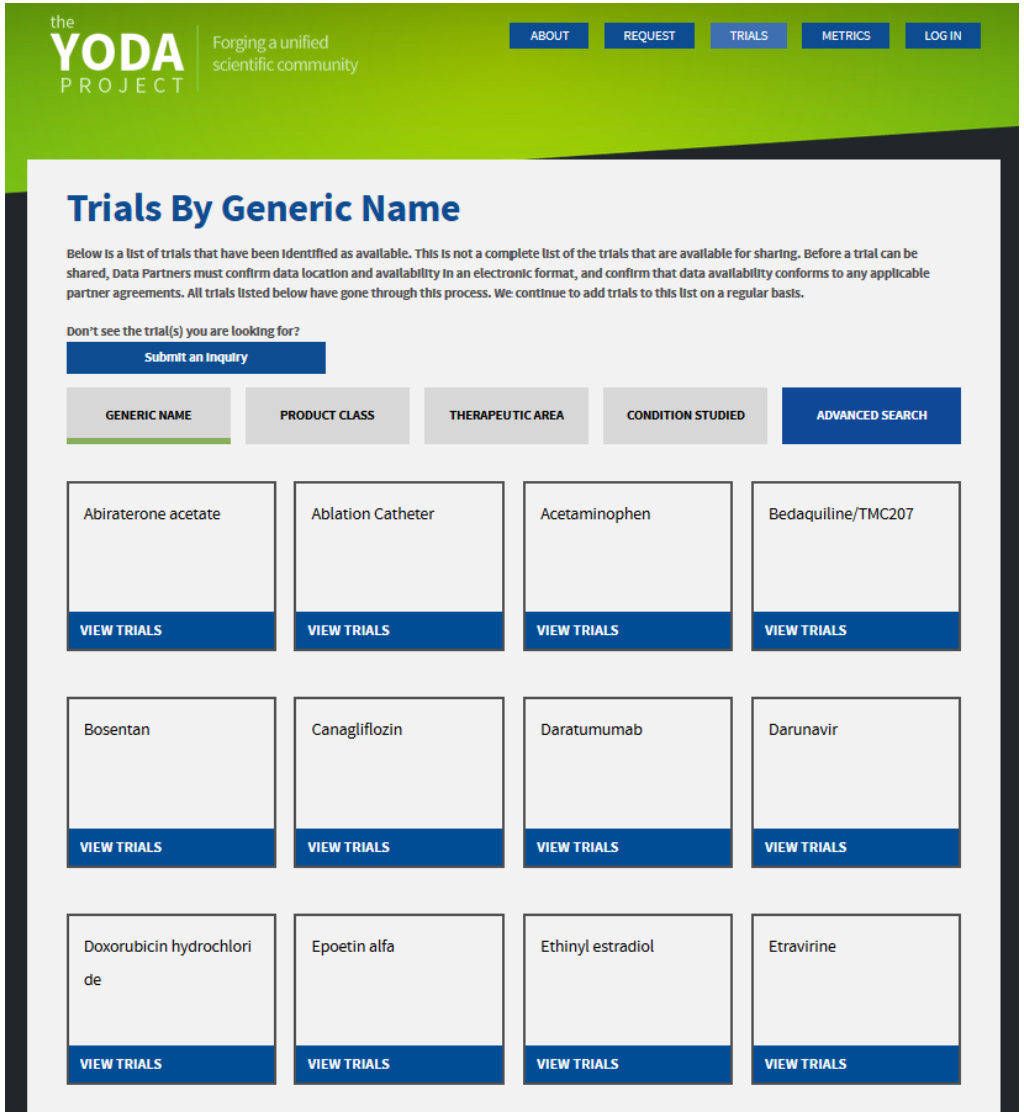
Source: Ross et. al. Scientific Data 2019;5:180268.

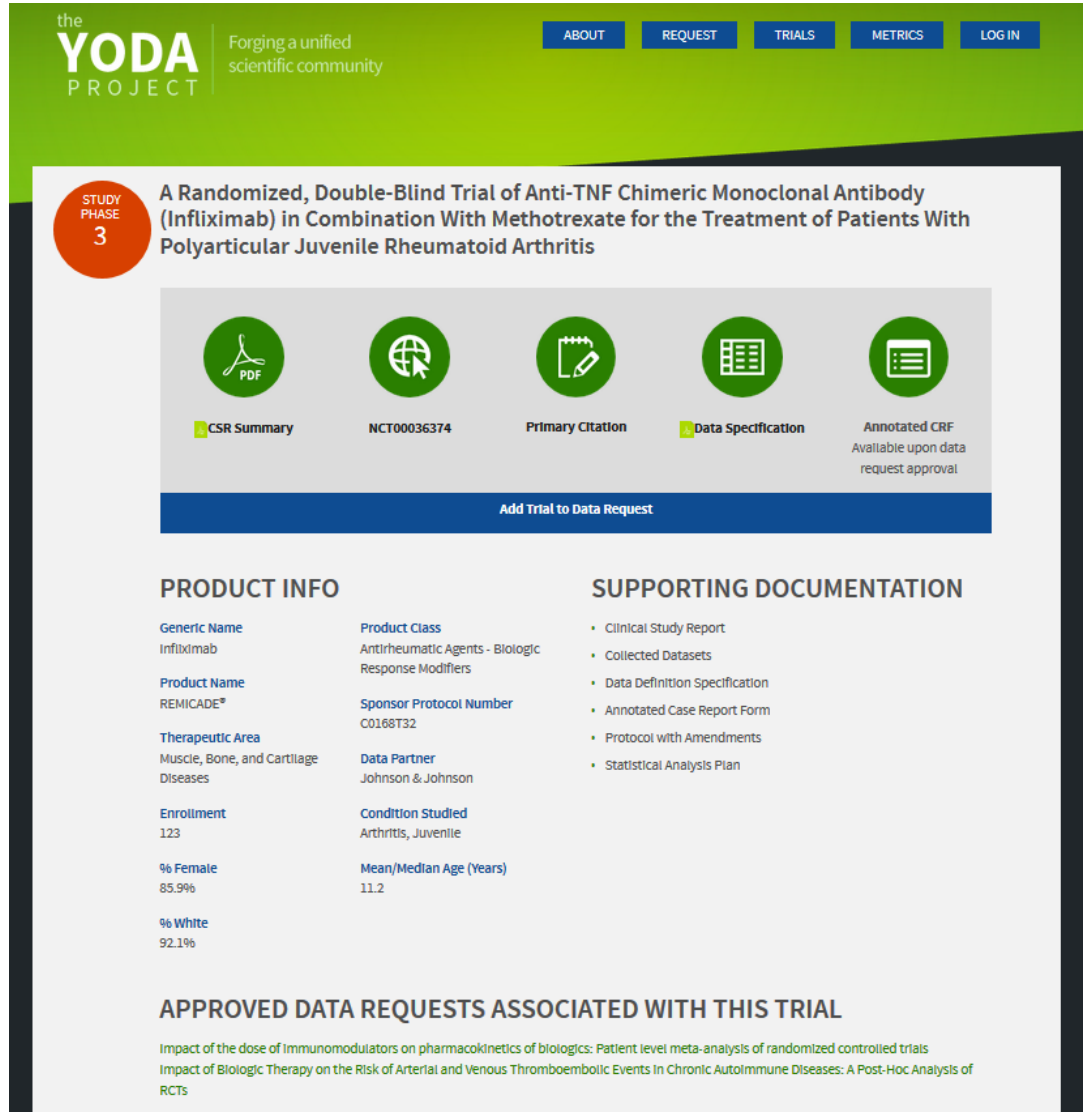
Principles of the YODA Project

- Promote sharing of clinical research data to advance science and improve public health and healthcare
- Promote responsible conduct of research
- Ensure good stewardship of clinical research data by external investigators
- Protect rights of research participants

Johnson & Johnson Partnership

- Initiated in 2014 – effort focused on promoting and facilitating access to clinical trial data:
  - All pharmaceutical products (including legacy trials)
  - Device and diagnostic products as of 2015
  - Consumer products as of 2017
- Established data access policy and procedures, with input from Steering Commitee, experts, stakeholders, and public comment





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Requests Submitted Online

- Investigator names, affiliations, funding
- Narrative summary / public abstract
- Detailed research proposal, including:
  - Project background, clear objectives
  - Trials, sample eligibility criteria, variables
  - Primary and secondary endpoints
  - Statistical analysis plan
- Project purpose (meta-analysis, validation …)
- Timeline and dissemination plan
- Data use agreement training

within 2 weeks

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YODA Project Review

The YODA Project reviews proposals to ensure that each proposal has scientific merit, specifically verifying:

- **Scientific purpose is clearly described**
- **Data requested will be used to create or materially enhance generalizable scientific and/or medical knowledge to inform science and public health**
- **Proposed research can be pursued using the requested data**

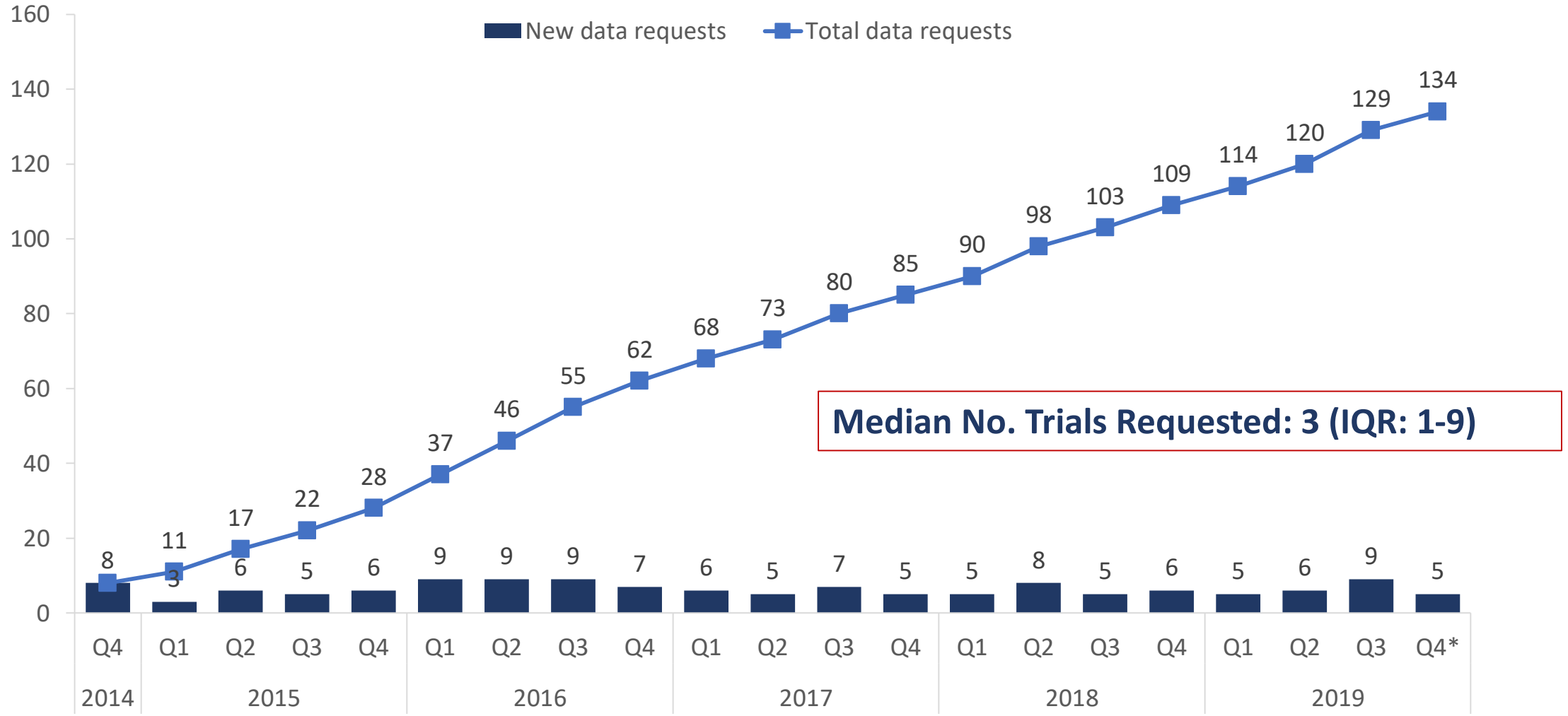
Data Partner Review

Requests for data undergo a Due Diligence Assessment by the Data Partner to evaluate their ability to make the data available to be shared, including assessment of:

- **Patient privacy**
- **Similar research studies**
- **Required variables**
- **Appropriateness of requested data (e.g. CSR vs IPD)**

- **Once approved, require signed DUA**
- **Investigators gain access to data maintained on secure platform, via VPN**
- **Prevents distribution, protects patient privacy**

Number of Data Requests Submitted



Median No. Trials Requested: 3 (IQR: 1-9)

*As of November 1, 2019

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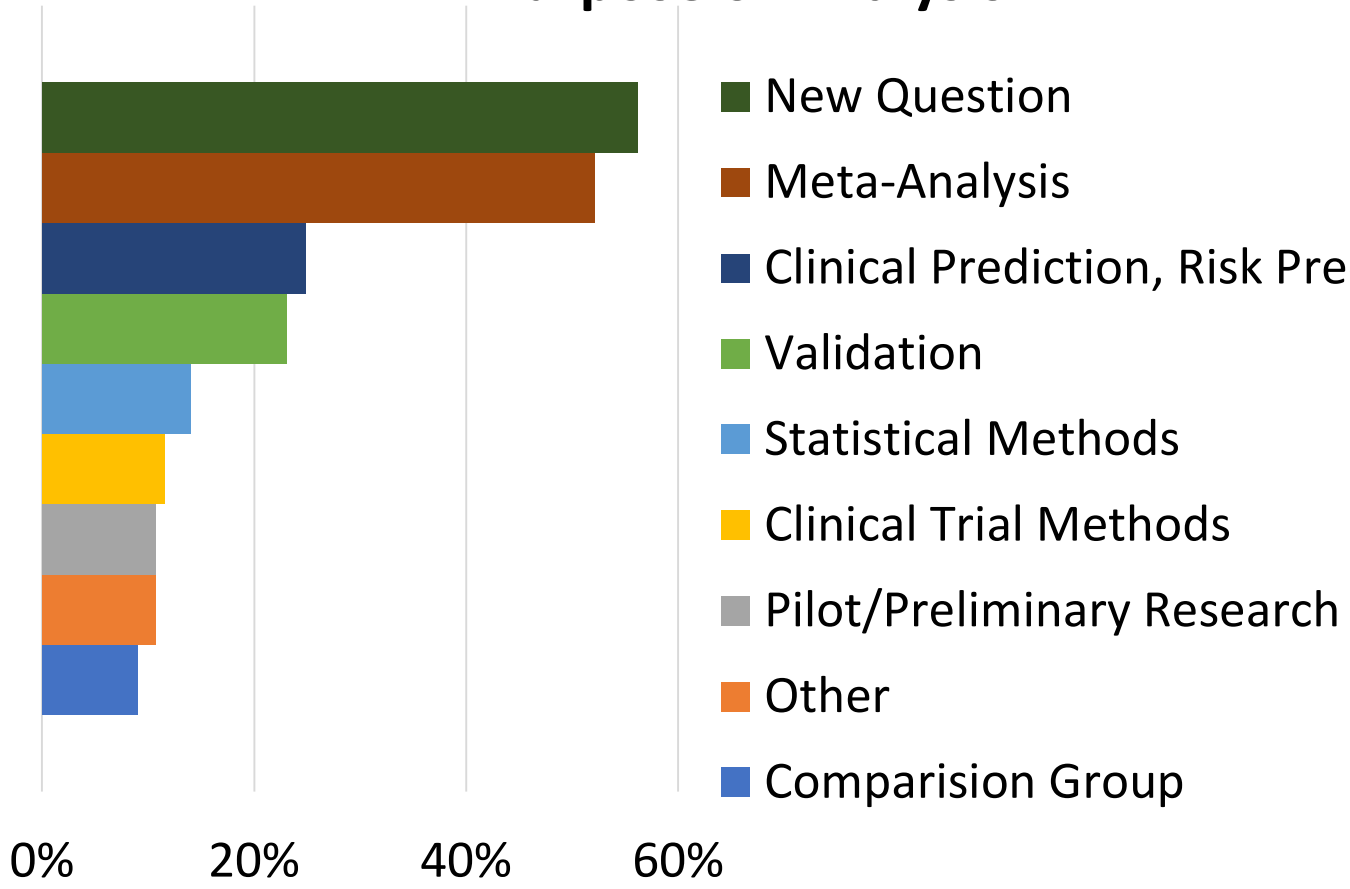
YODA Project Data Requests

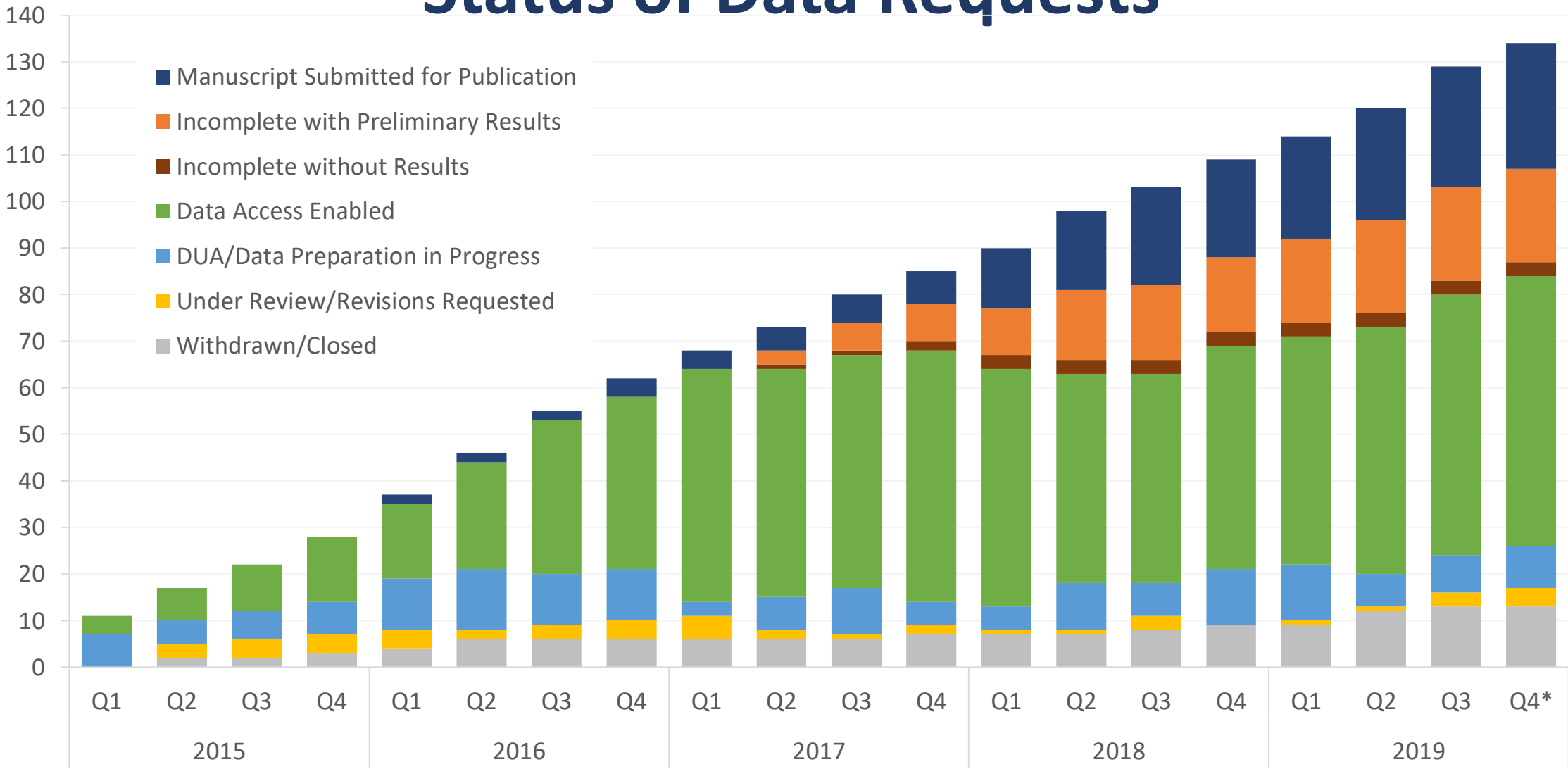
Purpose of Analysis



Researcher Affiliation

- **90% Academia**
- **5% Government**
- **4% Industry**
- **1% Other**

Status of Data Requests



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Approved Requests to Use Johnson and Johnson Data*

YODA Project Protocol Number	PI and Affiliation	Research Proposal	Product(s) of Interest	YODA Project Review and Data Partner Due Diligence Assessment	Project Status
2014-0340	**Heidl Storgaard, MD, PhD**; University of Copenhagan, Center for Diabetes Research	The effects of SGLT-2 inhibitors in patients with type 2 diabetes: a systematic review with meta-analysis of randomised trials	INVOKANA	YODA Project Review Due Diligence Assessment	Complete; Published in *PLOSONE* November 11, 2016.
2014-0333	**Guru Sonpavde, MD**; University of Alabama, Birmingham (UAB) School of Medicine	RECIST response as a surrogate endpoint in metastatic castration-resistant prostate cancer: Retro-spective analysis of COU-AA-203 and COU-AA-301	ZYTIGA	YODA Project Review Due Diligence Assessment	Unknown; data access revoked, investigator has not reported results as requested.
2014-0334	**Raymond Cross, MD, MS**; University of Maryland,	Gender differences in weight gain in patients with inflammatory bowel disease treated with Infliximab	REMICADE	YODA Project Review Due Diligence	Complete; Published in *Inflamm Bowel Dis* July 2, 2019.

*The YODA Project posts approved proposals once data access has been granted.

Submitted Data Requests Withdrawn/Not Approved*

The following data requests could not be fulfilled due to patient privacy concerns, data element availability, data security concerns, or lack of research proposal clarity.

YODA Project Protocol Number	PI and Affiliation	Research Proposal	Product(s) of Interest	YODA Project Review and Data Partner Due Diligence Assessment	Project Status
2014-0287	**William J. Sandborn, MD**; University of California, San Diego	Post hoc analysis of the ACT-1 & ACT-2 trials to simulate individualized dosing regimens using a predictive model	REMICADE	YODA Project Review Due Diligence Assessment	**Request originally approved but subsequently withdrawn: data could not be downloaded as requested*
2015-0406	**Nicola Schieda, MD FRCP(C)**; University of Ottawa	Is primary tumor in prostate cancer a reliable target lesion (measurable disease) at contrast-enhanced (CE) CT	ZYTIGA	YODA Project Review Due Diligence Assessment	**Request originally approved but subsequently withdrawn: CT scans not available due to patient privacy concerns*
2015-0501	**Anthony Otley, MD, MSc**;	Towards An Improved Pediatric Crohn's Disease	REMICADE	YODA Project Review	**Request originally*

*The YODA Project posts withdrawn/unapproved proposals at the time the decision is made.

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Experience so far …

- Of 350 trials currently listed on the site, 75% have thus far been requested (16 available only since July)
- Of 134 applications submitted, 117 (87%) approved, 4 (3%) remain under review; 13 (10%) withdrawn/closed
  - Usually because data not available/cannot be adequately de-identified
- Nearly all require some administrative revision, but 41 (31%) required scientific revision after review for clarity
- 31 manuscripts have been submitted for publication to peer-reviewed journals, 26 of which have been published
  - Thus far, 30% of projects with data access for ≥1 year published

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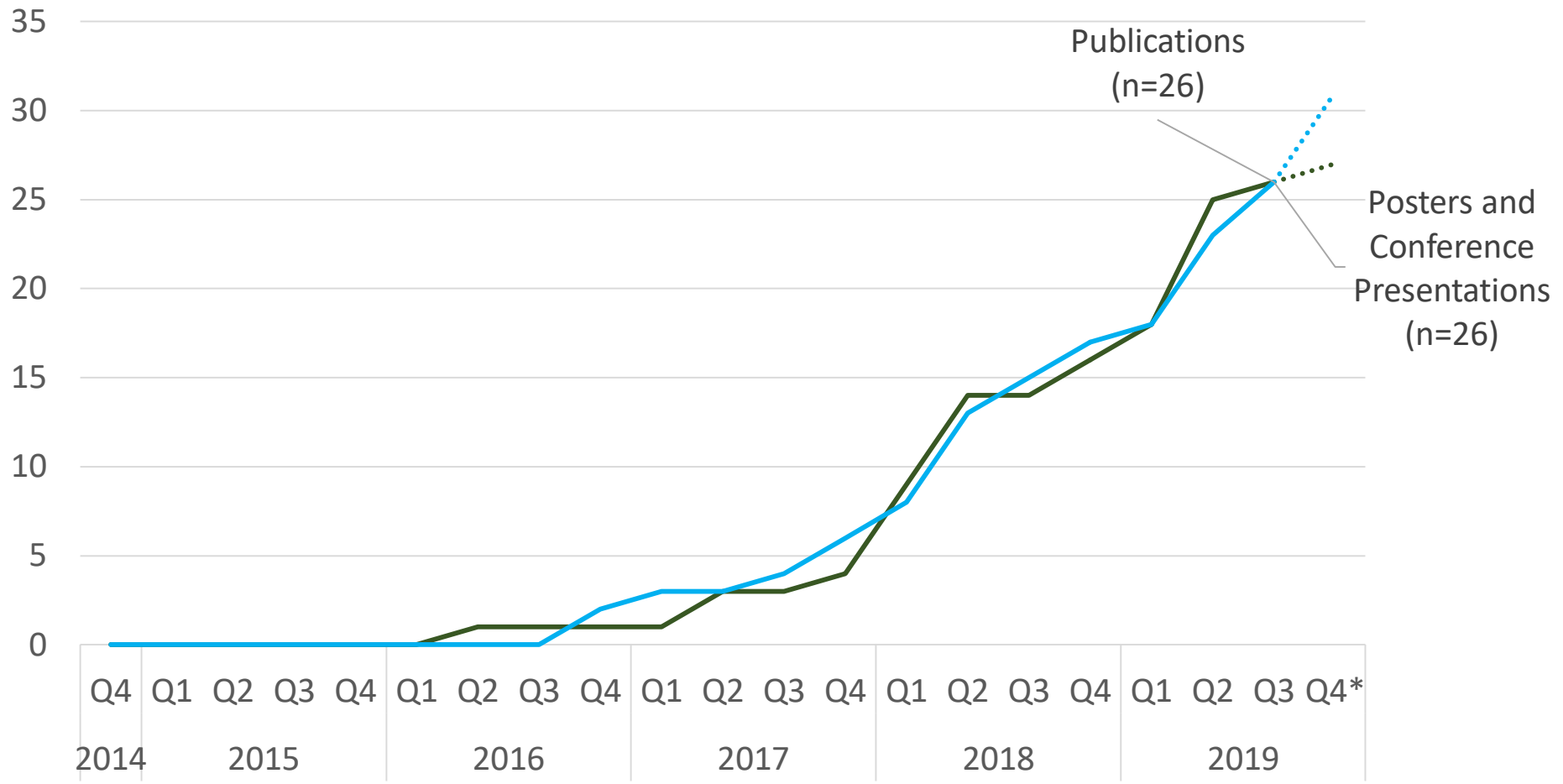
Publications and Posters (includes multiple per project)



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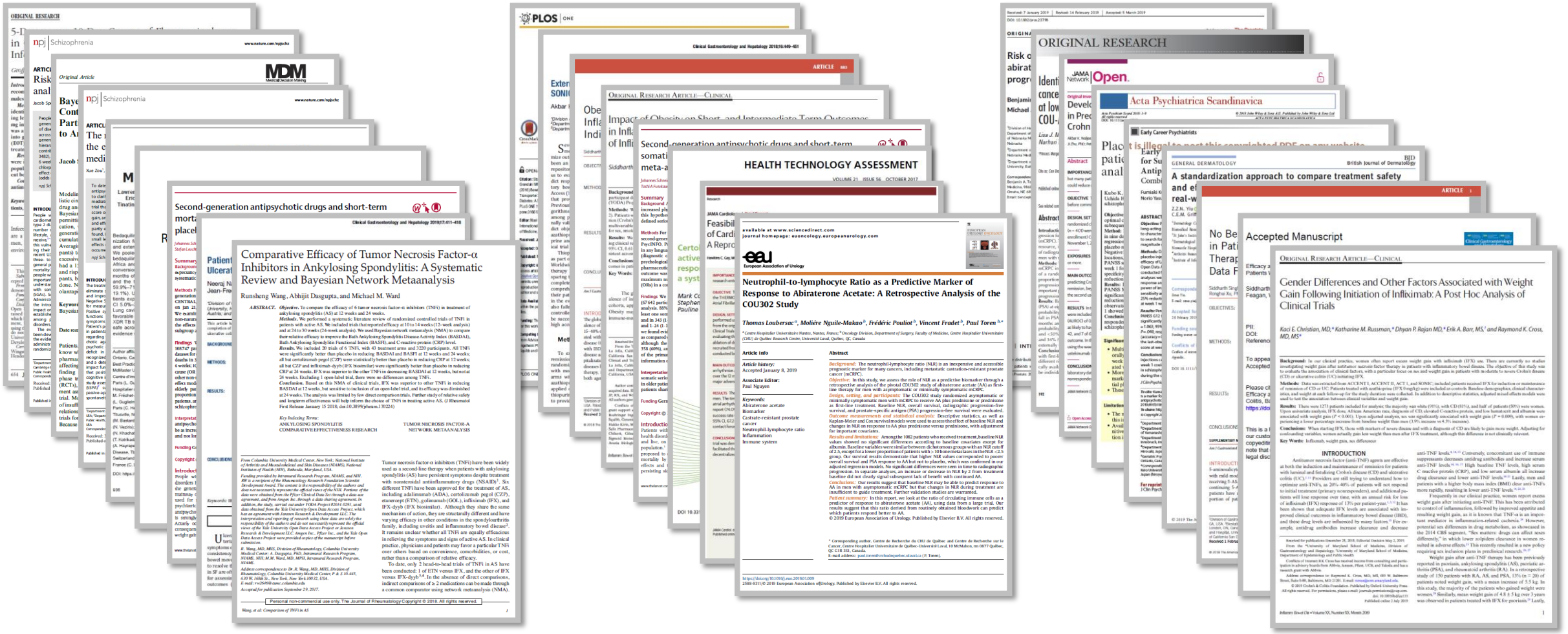
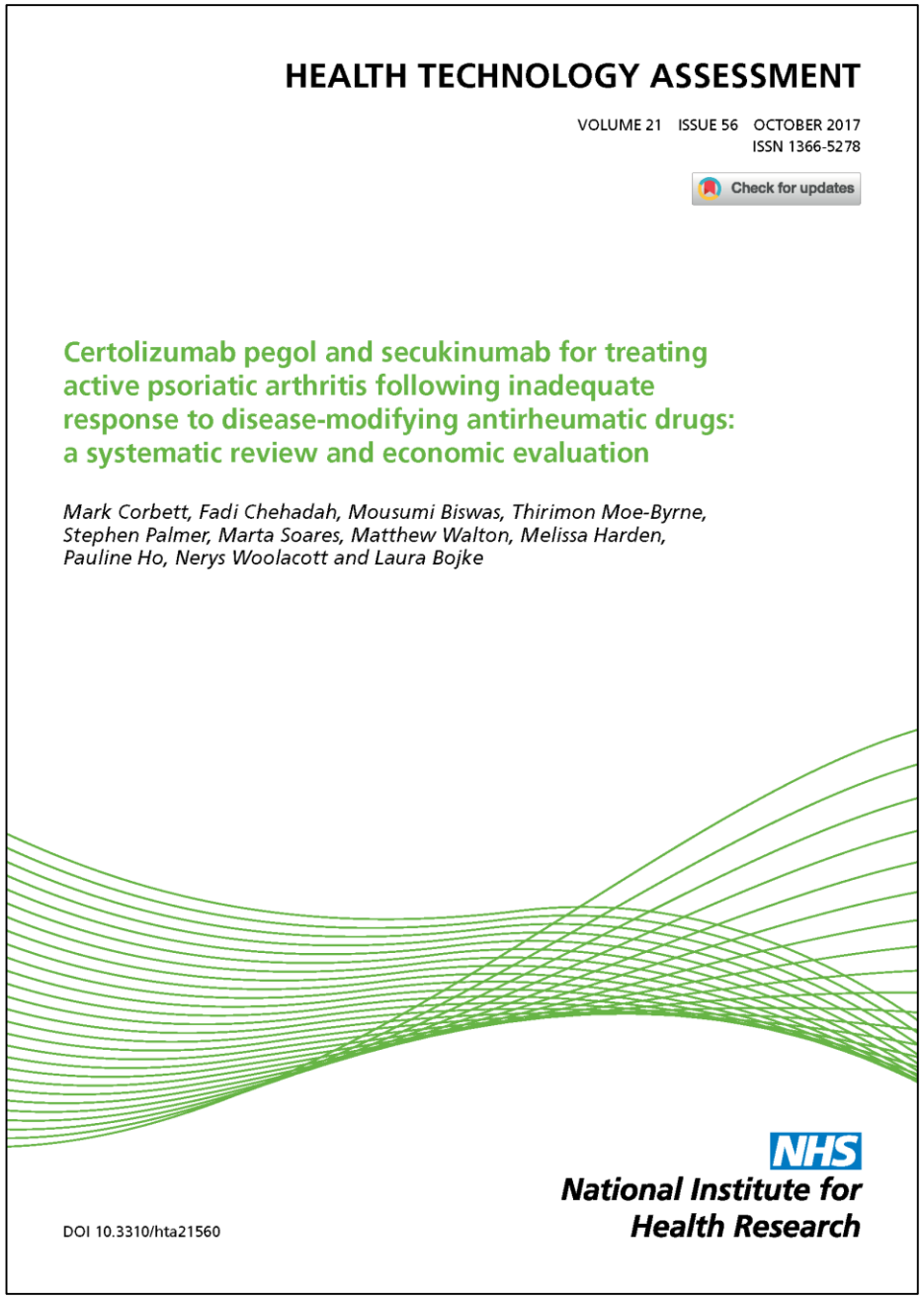
Articles Using Data Shared Through YODA Project





Objective: Assess the benefits, harms and cost-effectiveness of two new biologic therapies, compared to existing therapies:

- certolizumab pegol (CZP; CIMZIA®, UCB Pharma, Brussels, Belgium)
- secukinumab (SEC; COSENTYX®, Novartis International AG, Basel, Switzerland)

Key Findings: Both CZP and SEC are effective therapies for improving the symptoms of PsA. These new biologics can be considered a cost-effective use of NHS resources.

Review of available evidence on the use of bedaquiline for the treatment of multidrug-resistant tuberculosis: Data analysis report

Prepared for:
The World Health Organization

Prepared by:
Lawrence Mbuagbaw, MD, MPH, PhD
Assistant Professor
Department of Health Research Methods, Evidence and Impact,
McMaster University, Hamilton, Ontario, Canada

McMaster University
HEALTH RESEARCH METHODS, EVIDENCE, AND IMPACT

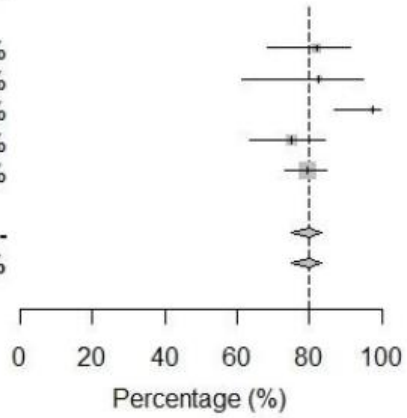
MARCH 8, 2017
VERSION 6

Objective: Review new evidence on the use of bedaquiline to inform changes in the World Health Organization (WHO) interim policy guidance on the use of bedaquiline for the treatment of multidrug-resistant tuberculosis (MDR-TB).

Key Findings: Bedaquiline effective for treatment of MDR-TB.

Study	Number	Total	Percentage (%)	95% CI	Weight
Armenia (N=62)	41	50	82.0	[68.6; 91.4]	12.6%
Georgia (N=30)	19	23	82.6	[61.2; 95.0]	5.6%
France (N=45)	40	41	97.6	[87.1; 99.9]	1.7%
South Africa (N=195)	54	72	75.0	[63.4; 84.5]	23.1%
Drug manufacturer (N=205)	163	205	79.5	[73.3; 84.8]	57.0%
Fixed effect model		**391**	**79.7**	**[75.2; 83.5]**	--
Random effects model			**79.7**	**[75.2; 83.5]**	**100%**

Heterogeneity: I2=38.7%, tau2<0.0001, p=0.1634



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PLOS ONE

RESEARCH ARTICLE

Benefits and Harms of Sodium-Glucose Co-Transporter 2 Inhibitors in Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis

Heidi Storgaard[1]*, Lise L. Gluud[2], Cathy Bennett[3], Magnus F. Grøndahl[1], Mikkel B. Christensen[1,4], Filip K. Knop[1,5,6], Tina Vilsbøll[1,5]

1 Centre for Diabetes Research, Gentofte Hospital, University of Copenhagen, Hellerup, Denmark, **2** Gastrounit, Copenhagen University, Hvidovre Hospital, Hvidovre, Denmark, **3** Centre for Technology Enabled Health Research, Coventry University, Coventry, United Kingdom, **4** Department of Clinical Pharmacology, Bispebjerg Hospital, University of Copenhagen, Copenhagen, Denmark, **5** Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark, **6** The Novo Nordisk Foundation Centre for Basic Metabolic Research, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

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OPEN ACCESS

Citation: Storgaard H, Gluud LL, Bennett C, Grøndahl MF, Christensen MB, Knop FK, et al. (2016) Benefits and Harms of Sodium-Glucose Co-Transporter 2 Inhibitors in Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis. PLoS ONE 11(11): e0166125. doi:10.1371/journal.pone.0166125

Editor: Noel Christopher Barengo, Florida International University Herbert Wertheim College of Medicine, UNITED STATES

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Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

Funding: The authors received no specific funding for this work.

Competing Interests: HS has received lecture fees from Advisory Boards of AstraZeneca, Boehringer Ingelheim Pharmaceuticals, and Bristol-Myers Squibb and has participated in Advisory Boards of

Abstract

Objective

Sodium-glucose co-transporter 2 inhibitors (SGLT2-i) are a novel drug class for the treatment of diabetes. We aimed at describing the maximal benefits and risks associated with SGLT2-i for patients with type 2 diabetes.

Design

Systematic review and meta-analysis.

Data Sources and Study Selection

We included double-blinded, randomised controlled trials (RCTs) evaluating SGLT2-i administered in the highest approved therapeutic doses (canagliflozin 300 mg/day, dapagliflozin 10 mg/day, and empagliflozin 25 mg/day) for ≥12 weeks. Comparison groups could receive placebo or oral antidiabetic drugs (OAD) including metformin, sulphonylureas (SU), or dipeptidyl peptidase 4 inhibitors (DPP-4-i). Trials were identified through electronic databases and extensive manual searches. Primary outcomes were glycated haemoglobin A1c (HbA1c) levels, serious adverse events, death, severe hypoglycaemia, ketoacidosis and CVD. Secondary outcomes were fasting plasma glucose, body weight, blood pressure, heart rate, lipids, liver function tests, creatinine and adverse events including infections. The quality of the evidence was assessed using GRADE.

Results

Meta-analysis of 34 RCTs with 9,154 patients showed that SGLT2-i reduced HbA1c compared with placebo (mean difference -0.69%, 95% confidence interval -0.75 to -0.62%). We

Objective: Determine benefits and risks associated with SGLT2-i for patients with type 2 diabetes mellitus.

Key Findings: SGLT2-i reduced HbA1c when compared with placebo.

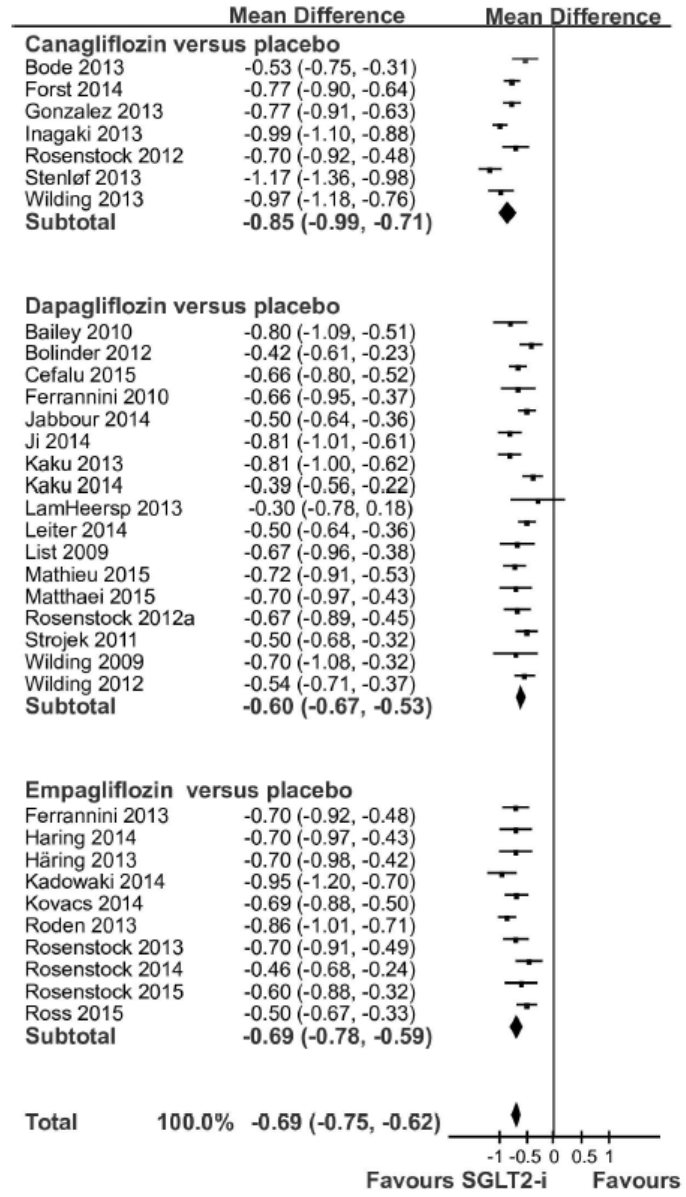

Fig 2. Change in glycated haemoglobin: forest plot of randomized controlled trials comparing sodium-glucose co-transporter 2 inhibitors (SGLT2-i) versus placebo. The plot shows subgroups of trials assessing the different SGLT2-i.

Strengthening Science through Data Sharing

- Numerous studies that might not otherwise have been feasible to pursue, some of which have impacted health policies and guidelines
- Facilitated direct collaborations with original investigators
- Developed efficiencies (J&J now conducts all trials intending to share)
- Replication studies have supported – not undermined – original study
- No instances of patient privacy breaches
- No publications of spurious safety findings that received unwarranted attention or disrupted patient care
- No data have been used for commercial or litigious purposes

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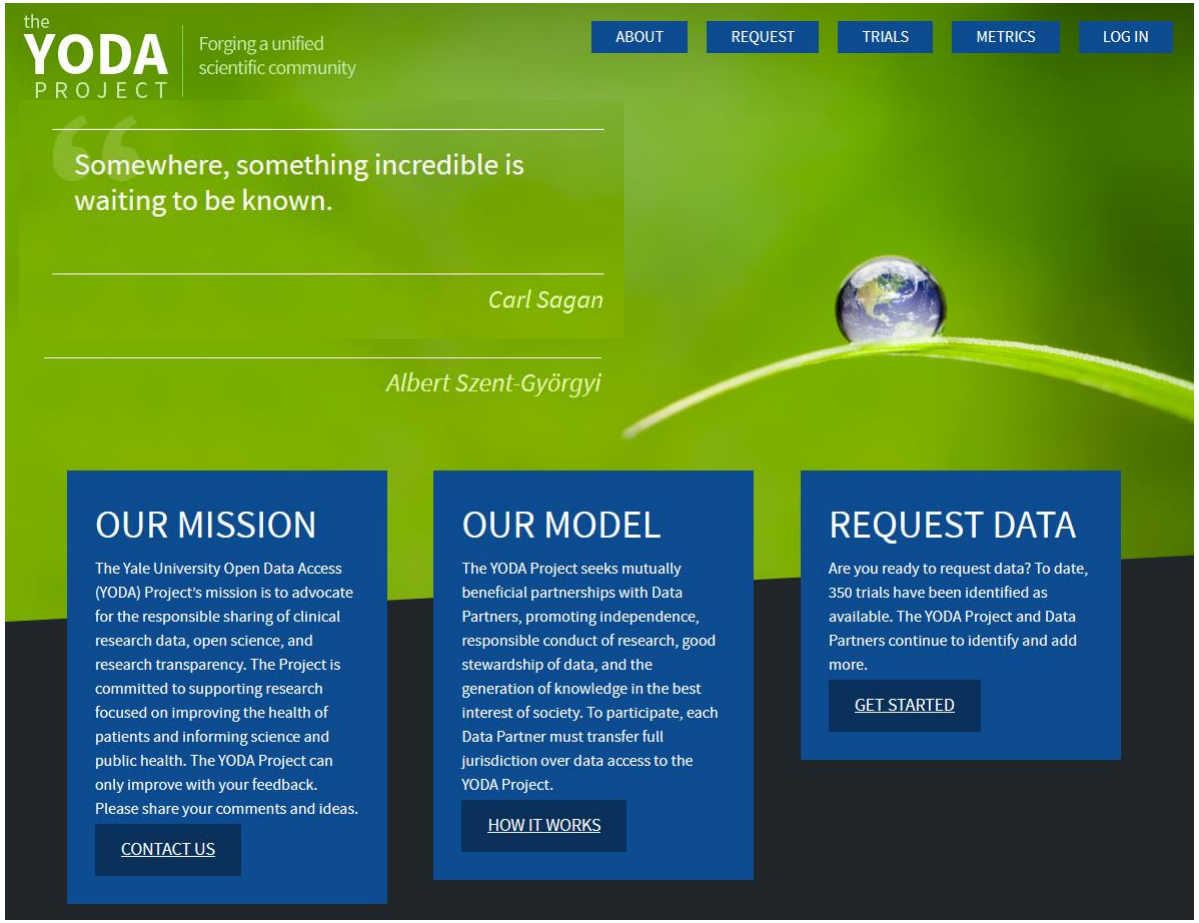
Challenges Remain

- Broadening awareness of data availability
- Fostering expertise in using data from clinical trials (*it's complicated*)
- Making older trial data available in a contemporary format
- Adopt data standards, across sponsors, to enable meta-analyses
- Sustainable model that covers the cost of data sharing
- Data Use Agreements …
- Establish standards: when should data be available, for how long, how to reward those who share data?
- Many large pharma sharing, what about other sponsors?



http://yoda.yale.edu

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We've Learned and Iterated with Experience …

- Transparency
- Full authority and independence
- Independent Steering Committee
- Public list of available trials
- Supporting documentation
- Research proposal submission and public posting
- Blinded review of requests by the YODA Project and partnering company
- Opportunity for collaboration with partnering company
- Data Use Agreement
- Secure data access or transfer
- Results dissemination
- No data access fee

Benefits of Sharing Early Clinical Research Data

- Ensures all data can be used to inform clinical decisions
- Positions research as a public good
- Respects contributions of participants:
  - maximizing value of collected data, while
  - minimizing duplicative data collection
- Facilitates secondary studies of existing data
- Promotes transparency and reproducibility:
  - sample, design, and analysis