COVID-19 Vaccine Clinical Trials
Vivli: The Difference Data Re-Use Can Make
Agenda

- Overview of clinical trial data sharing
- How can Vivli help me share my clinical study data?
- How can I request data from other completed studies?
Today’s Menu of Crohn’s Treatments

- **Infliximab** (TNFi, 1998)
- **Natalizumab** (anti-α_4, 2004)
- **Adalimumab** (TNFi, 2007)
- **Certolizumab** (TNFi, 2008)
- **Ustekinumab** (anti-IL12/23, 2016)
- **Vedolizumab** (anti-α_4β_7, 2014)
- **Surgery**
Questions, questions...

<table>
<thead>
<tr>
<th>Trials</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRECISE 1/2</td>
<td>Certolizumab</td>
</tr>
<tr>
<td>CLASSIC 1/2</td>
<td>Adalimumab</td>
</tr>
<tr>
<td>GEMINI 2</td>
<td>Vedolizumab</td>
</tr>
<tr>
<td>ENACT</td>
<td>Natalizumab</td>
</tr>
<tr>
<td>ACCENT 1/2</td>
<td>Infliximab</td>
</tr>
<tr>
<td>UNITI</td>
<td>Ustekinumab</td>
</tr>
<tr>
<td>CERTIFI</td>
<td>Ustekinumab</td>
</tr>
</tbody>
</table>

**Efficacy questions**

- Are there subgroups that preferentially respond to some drugs over others?
- How much time do we need to confidently determine if a patient will favorably respond? What data do we need to make this determination?

**Safety**

- Are there certain subgroups more susceptible to certain severe adverse effects (SAEs) than others?
- What does this tell us about the biology of SAEs as they relate to drug mechanism of action?
Getting to Answers...

Vivli Pioneer Award Winner

Question: In the absence of head-to-head randomized trials, can we determine which Crohn’s treatments are better than others (and in whom)?

Current approach:
• Summary-level meta-analysis

• Cons: differences in doses, treatment durations, definitions of response, allowed concomitant medications, trial designs, underlying cohorts, ecological fallacy, etc.
Getting to Answers…

Summary-level Meta-analysis

Individual Participant-Level Meta-Analysis

North

Summary-level Meta-analysis

Exit 310

West

Individual Participant-Level Meta-Analysis

Exit Only
Evolution of Clinical Trial Data Sharing

Clinical trials registration
- ICMJE requirement for publication (2004)
- FDAAA requirement for applicable trials (2007)

Summary data shared
- EU no. 536/2014 requires lay summaries (effective late 2020)

Clinical Study reports - CSRs & Individual Participant Data (IPD) shared
- Health Canada Regulations (2019) (IPD not included)
- PhRMA/EFPIA principles for data sharing (2014)
- IOM Sharing Clinical Trial Data report (2015)

2004
2016
2018...
2018: Major Journals Require IPD Sharing Statement

- Trial manuscript submissions must include a data sharing statement
  - who, what, when, where, and why and how IPD will be shared
- Some journals routinely request IPD be shared
  - e.g., BMJ, PLoS Medicine, Lancet

ICMJE: International Committee of Medical Journal Editors
Mid-2018: Vivli Launches

- **2019**
  - 2500+ Participants from 98 countries
  - 4700+ Trials
  - 15 Members

- **2020**
  - 5800+ Participants from 109 countries
  - 3.6M Participants from 119 countries
  - 29 Members
2019: Data Sharing Plans at Trial Registration

- Data sharing plans added to ClinicalTrials.gov registration
- ICMJE requires that you included a data sharing plan at time of trial registration

12. IPD Sharing Statement

Plan to Share IPD
Definition: Indicate whether there is a plan to make individual participant data (IPD) collected in this study, including data dictionaries, available to other researchers (typically after the end of the study). Select one.
- Yes: There is a plan to make IPD and related data dictionaries available.
- No: There is not a plan to make IPD available.
- Undecided: It is not yet known if there will be a plan to make IPD available.

IPD Sharing Plan Description
Definition: If Plan to Share IPD is "Yes," briefly describe what specific individual participant data sets are to be shared (for example, all
2023: NIH Requiring Data Sharing Plans

• Data sharing plan must be included in NIH grant proposals
  - but will not be scored as part of peer review
• Allowed to budget for data sharing costs
• Encourages use of established repositories (including Vivli)
Benefits of IPD Sharing

- **Honors** the commitments of participants
- **Strengthens trust** in the clinical research enterprise
- **Prevents repetitive trials** and putting additional patients at risk
- **Enables new discovery** and scientific insights through combining data from disparate sources
"The 48% of trials with publicly available microarray data received 85% of the aggregate citations. Publicly available data was significantly (p = 0.006) associated with a 69% increase in citations"
Introducing Vivli

THE ENTITY

• Non-profit organization
• Convening function
  - Biomedical industry (pharma, bio, device)
  - Academia
  - Non-profit funders and foundations
  - Government (funders and regulators)
  - Patient/patient advocates
• Governance and policy
  - Harmonizing language & agreements
  - Move culture of data sharing
• Advocacy
  - Lowering barriers
  - Promoting incentives
• Oversight of Implementation

THE PLATFORM

• A user-friendly, secure, state-of-the art data sharing and computing platform
• Serving the international community, including trials from any disease, country, sponsor, funder, or investigator
  - Open search
  - Robust security
  - Modern tools and technologies
HOW TO SHARE DATA VIA VIVLI
Balancing Risks and Benefits

Openness

Maximizing the value of the data collected respects participants’ contributions

Privacy

Protecting participant privacy
# Approaches to Sharing Human Data

<table>
<thead>
<tr>
<th>Type</th>
<th>Key Features</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open access</td>
<td>Anyone can access, simple account creation, simple on-line data use agreement (DUA)</td>
<td>Health CAN, EMA, Project Datasphere</td>
</tr>
<tr>
<td>Managed access</td>
<td>• for scientific purposes only (standard request form)</td>
<td>Vivli, CSDR, SOAR, VISTA</td>
</tr>
<tr>
<td></td>
<td>• (independent) review process</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• secure environment for data access</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• clear legal framework</td>
<td></td>
</tr>
<tr>
<td>Restricted access</td>
<td>Invitation only, access only to those who provide data</td>
<td>DataCelerate, IBD Plexus</td>
</tr>
</tbody>
</table>
Vivli Members
## When to Use Vivli

<table>
<thead>
<tr>
<th>Data Contributors</th>
<th>IPD Sharing Requirements</th>
<th>Figshare &amp; Dryad</th>
<th>Internal University Repositories</th>
<th>“Walled Gardens”</th>
<th>Vivli</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IPD can be stored and securely hosted</td>
<td>✔️</td>
<td>✔️</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Harmonized data contributor and data use agreements</td>
<td>✔️</td>
<td></td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td></td>
<td>IPD can be shared <strong>securely</strong> to anyone in the world</td>
<td></td>
<td>✗</td>
<td></td>
<td>✔️</td>
</tr>
<tr>
<td></td>
<td>Independent request review available</td>
<td></td>
<td></td>
<td></td>
<td>✔️</td>
</tr>
<tr>
<td>Data Users</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>One-stop shop for finding IPD on any therapeutic area from any contributor worldwide</td>
<td></td>
<td>✗</td>
<td></td>
<td>✔️</td>
</tr>
<tr>
<td></td>
<td>Harmonized data request form</td>
<td></td>
<td></td>
<td></td>
<td>✔️</td>
</tr>
<tr>
<td></td>
<td>Additional data and software can be brought into the research environment</td>
<td></td>
<td></td>
<td></td>
<td>✔️</td>
</tr>
<tr>
<td></td>
<td>Uniform security standards and policies</td>
<td></td>
<td></td>
<td></td>
<td>✔️</td>
</tr>
</tbody>
</table>
IPD Sharing over Study Lifecycle

IPD Data Package required contents

- IPD
- Protocol
- Data Dictionary
- Statistical Analysis Plan

Optional: Informed consent, case report form, analytic code...
Protecting private or sensitive information by perturbing data

• De-identification: identifiers are removed to reduce the risk that a person can be re-identified from the data
• Anonymization: erasing or encrypting all identifiers that connect an individual to stored data

Privacy Analytics partnership

• Special discounted pricing and turn around time for Vivli members (industry sponsors and academics)
• Secure and audited environment for performing the anonymization
• Risk-based quantitative anonymization approach: consistent with current best practices as recommended by EMA and Health Canada
Data Contributor Agreement – Key provisions

Key Vivli DCA provisions.

Researcher agrees

• The data are provided in an anonymized form (meaning that measures have been taken to reduce the risk of re-identification of individual participants)
• Researcher has the rights to share the data and continues to maintain pre-existing ownership rights

Vivli agrees – That Recipients must sign the DUA for access
Data Use Agreement – Key provisions

- Vivli manages DUA process for members who use the Vivli harmonized DUA
- Vivli members who are partner platforms may use their own DUA as long as it does not conflict with the Vivli DUA (cross-platform sharing)

**Key Vivli DUA provisions. Researcher agrees:**
- To adhere to a research plan
- To make reasonable efforts to publish
- Not to re-identify participants
## Costs Per Study

<table>
<thead>
<tr>
<th>Study Curated and Listed on Vivli</th>
<th>Anonymized IPD Storage</th>
<th>Independent Review Panel</th>
<th>One-off Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study ready for sharing and needs storage</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Study ready for sharing and needs Storage and Independent Review Panel</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Anonymization</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>
Institutional Membership

• Institutions can join Vivli as a member
  - covers data depositions from that institution

• Steps
  1. Sign membership agreement
  2. Agree to harmonized Data Contributor Agreement / Data Use Agreement (DCA/DUA)
  3. Post membership page on Vivli website explaining how requests will be reviewed, etc.

• Contact jwood@vivli.org
IPD Package is Listed and Requestable

Grant Submission
- Data sharing plan in proposal

Trial Registration
- Data sharing plan in registration

Trial Completion
- Archive IPD Data Package in Vivli

Publication
- Summary results to CT.gov
- Data sharing plan to journal

12 Months Later

Embargo Period

Searchable
- Listed on Vivli

Requestable
- Available for requests

Shared
- IPD reused, tracked
Informed Consent and IPD Sharing

• Typically, data are shared in “de-identified” or “anonymized” form
• Vivli accepts only anonymized data
• The extent to which consent remains relevant following de-identification or anonymization is a debated issue
• Common view is that promises made to research subjects at the time of consent must be respected, regardless of whether data have been de-identified or anonymized
Informed Consent explicitly prohibits secondary uses of data

“your trial data from the XYZ breast cancer study will be made available to XYZ investigators at UCSF and regulators who may need to review your data for regulatory purposes.”

• Implies that data would not be shared beyond original trial purpose (even if anonymized)
• Best practice would recommend not using this data for secondary research purposes
• Participants may be re-consented for secondary uses of their data
ICF is **silent** regarding secondary uses of data (**most common**)

- No explicit promises were made to the contrary, secondary uses of data are thought permissible if the data are “anonymized” or “de-identified”
  - Consider additional consent / notice requirements of particular regulatory regime

- Increasing trend to require notice of and/or consent to future uses of de-identified or anonymized data (**Revised Common Rule**)
HOW TO REQUEST DATA VIA VIVLI
Agnostic to Disease, Funder or Data Contributor
We are committed to advancing the knowledge around the COVID-19 pandemic

All fees are waived for sharing and accessing clinical trials

Share trials
Search for trials

What are you looking for today?

STUDY DESIGN
INTERVENTIONAL STUDIES
Select Multiple

OBSERVATIONAL STUDIES
Select Multiple

SPONSOR INFORMATION
SPONSOR TYPE
Select Multiple

SPONSOR
Select Multiple

STUDY PHASE
Select Multiple

SAMPLE SIZE

LOCATION
Select Multiple

START DATE
FROM TO
mm/yyyy mm/yyyy

END DATE
FROM TO
mm/yyyy mm/yyyy

5811 Studies
### 18 Therapeutic Areas Covered by Vivli Requests

<table>
<thead>
<tr>
<th>TYPE</th>
<th>Number of Requests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>25</td>
</tr>
<tr>
<td>Dermatology</td>
<td>7</td>
</tr>
<tr>
<td>Endocrinology</td>
<td>6</td>
</tr>
<tr>
<td>Gastroenterology</td>
<td>9</td>
</tr>
<tr>
<td>Hematology</td>
<td>3</td>
</tr>
<tr>
<td>Infectious Disease</td>
<td>5</td>
</tr>
<tr>
<td>Methods</td>
<td>12</td>
</tr>
<tr>
<td>Neurology</td>
<td>25</td>
</tr>
<tr>
<td>Oncology</td>
<td>52</td>
</tr>
<tr>
<td>Orthopedics</td>
<td>5</td>
</tr>
<tr>
<td>Psychiatry</td>
<td>13</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>18</td>
</tr>
<tr>
<td>Rheumatology</td>
<td>30</td>
</tr>
<tr>
<td>Other</td>
<td>7</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>217</strong></td>
</tr>
</tbody>
</table>

215 Requests as of November 2020
Types of Planned Secondary Research

- New Research: 36%
- IPD Meta-Analysis: 25%
- Preliminary Research: 17%
- Confirmatory Research: 6%
- Summary M-A: 4%
- Other: 12%

N = 215
NIDDK-related studies on Vivli

- 400+ studies available in NIDDK-related fields

- Sample of requests already approved related to NIDDK
  1. **Chronic Kidney Disease** Epidemiology – Clinical Trials Consortium (CKD-EPI CT)
  2. **TRIAL-INFORMED DKA MITIGATION EDUCATIONAL TOOL**
  3. **Stratification of SGLT2 inhibitor glucose lowering therapy in Type 2 diabetes**
  4. **The impact of biological interventions on health-related quality of life in adults with Crohn's disease**
  5. **Predictors of Mucosal Healing in Ulcerative Colitis: A Post-hoc Analysis of VARSITY**
7 of the most requested studies on Vivli are in IBD

<table>
<thead>
<tr>
<th>Gastroenterology</th>
<th>Crohn's Disease</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>UC</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Rheumatology</th>
<th>RA</th>
<th>14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiology</td>
<td>AFIB</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Stroke</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Bladder</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Oncology</th>
<th>Breast</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NSCLC</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>RCC</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Covid 19</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other</th>
<th>Depression</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Duchenne</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Hidradinitis</td>
<td>2</td>
</tr>
</tbody>
</table>

400+ NIDDK topic studies available for request
Getting to Answers...

Vivli Pioneer Award Winner

All phase 2/3, completed, randomized, double-blinded, placebo-controlled, trials of FDA-approved drugs for moderate-to-severe Crohn’s Disease (at the FDA-approved dose) in adults, extending to at least 24 weeks in duration

Dr. Vivek Rudrapatna
Assistant Professor, UCSF
Requesting IPD

**REQUEST**

Request IPD Data sets.

Each Data Request will be **reviewed** according to contributors' publicly stated requirements.

**REVIEW**

Reviewed by sponsor or independent review panel.

Sponsor provides IPD, data dictionary, protocol, statistical analysis plan.

**ACCESS**

Data from approved requests can be **accessed** in Vivli's secure research environment or **downloaded** with permission.

**ANALYZE**

Use robust **analytical tools** to combine and analyze multiple data sets.

**DISSEMINATE**

Completed research results will be assigned a DOI.

Researchers may use the Vivli platform to meet their **publication** requirements.
## Studies Requested; IPD Obtained

<table>
<thead>
<tr>
<th>Trials</th>
<th>Drug</th>
<th>Sponsor</th>
<th>Original Data Sharing Platform</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRECISE 1/2</td>
<td>Certolizumab</td>
<td>UCB</td>
<td>CSDR</td>
</tr>
<tr>
<td>CLASSIC 1/2</td>
<td>Adalimumab</td>
<td>AbbVie</td>
<td>Vivli</td>
</tr>
<tr>
<td>GEMINI 2</td>
<td>Vedolizumab</td>
<td>Takeda</td>
<td>Vivli</td>
</tr>
<tr>
<td>ENACT</td>
<td>Natalizumab</td>
<td>Biogen</td>
<td>Vivli</td>
</tr>
<tr>
<td>ACCENT 1/2</td>
<td>Infliximab</td>
<td>Janssen</td>
<td>YODA</td>
</tr>
<tr>
<td>UNITI</td>
<td>Ustekinumab</td>
<td>Janssen</td>
<td>YODA</td>
</tr>
<tr>
<td>CERTIFI</td>
<td>Ustekinumab</td>
<td>Janssen</td>
<td>YODA</td>
</tr>
</tbody>
</table>

Individual participant-level data (IPD) from **5011** patients in **10** trials
Vivli Secure Environment Bridges Multiple Platforms

BYO data, scripts, software on request

30+ tools
• SAS
• STATA
• MS Office
• R, + over 300 pkgs
• Jupyter Notebook
• Python, + over 250 pkgs
• Spark
• Anaconda
Vivli FAIR Data Sharing

• Findable
  - metadata model, annotated using Cochrane vocabulary (SNOMED, WHO ATC, MedDRA)
  - Dataset DOIs minted by DataCite

• Accessible
  - from fully downloadable to available only in secure MS Azure environment

• Interoperable, Reusable
  - SDTM format recommended but not required
  - No requirement for common variables
Outcomes of Vivli Data Sharing

- 10 publications so far (1st data requests submitted July 2018)
  - e.g., JNCI, Annals of Oncology, Clin Exp Dermatol, J Am Acad Derm, Ann of Rheum Dis, BMC Medicine

- Scientific value: case example of hidradenitis suppurativa

“I was at a conference in Europe last month and a half a dozen speakers were citing my research as the basis for re-thinking trial designs and the outcome measures used and whether multiple measures need to used or a new one developed to take these findings into account.”

“Having all this data available via the Vivli platform is a key tenet to evaluating the epidemiological aspects of this condition. This is beyond valuable.”

Dr. John Frew
Rockefeller University
CHALLENGES/FUTURE
Can Data Sharing Drive Common Biomarker Development and Adoption?

- PhenX, ICHOM, NIH CDE Repository contains over 27,000 CDEs
  - limited adoption overall
- Data sharing and re-use makes effort of Common Biomarkers directly visible and scientifically valuable
- Most successful when led by disease-specific investigator communities e.g.,
  - Traumatic Brain Injury
  - pediatric obesity

Challenges in Sharing of Clinical Trial Data (Individual Participant Data - IPD):

- Utilization lags behind data contribution
- Academic participation
- Data harmonization
- Awareness of data sharing initiatives
Summary

Vivli distinguishing features

• Trusted venue for sharing with the entire scientific community (not a “walled garden”)
• Established working relationships across industry, academia, and non-profit and government funders
• Enables data from multiple sources to be combined securely
• Given the urgency, we will support sharing of some interim participant-level data followed by the final dataset

Contact support@vivli.org
Explore Vivli

Log on to Vivli.org

To explore the ~5,800 trials and begin the search