Welcome to the OHDSI Face-to-face NYC 2018

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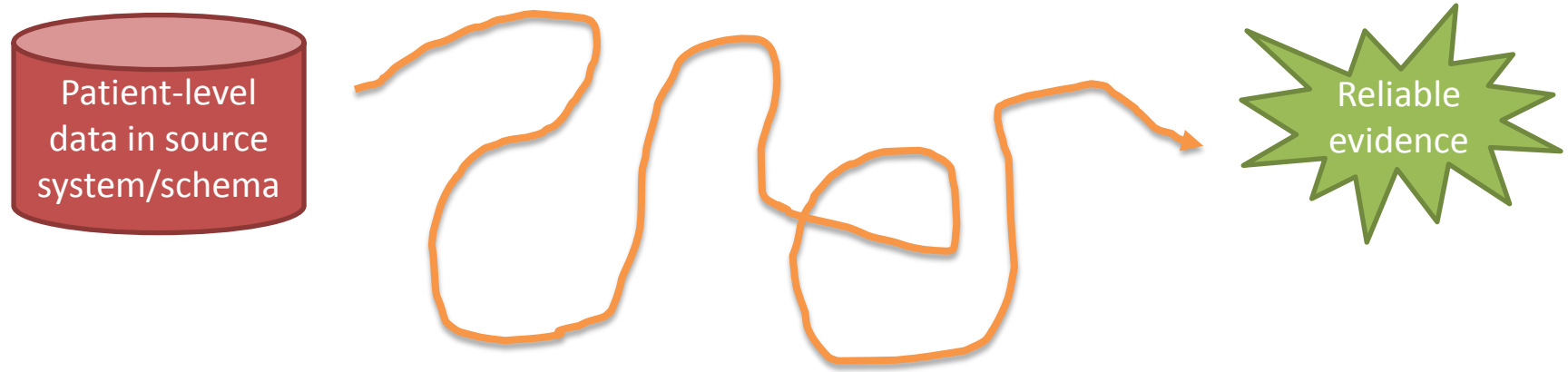
Why are we here?

Take 10 minutes to complete survey

Look in your email for note from Maura/Kristin or go to:

https://goo.gl/forms/nkYtjBmgWcghUDsH3

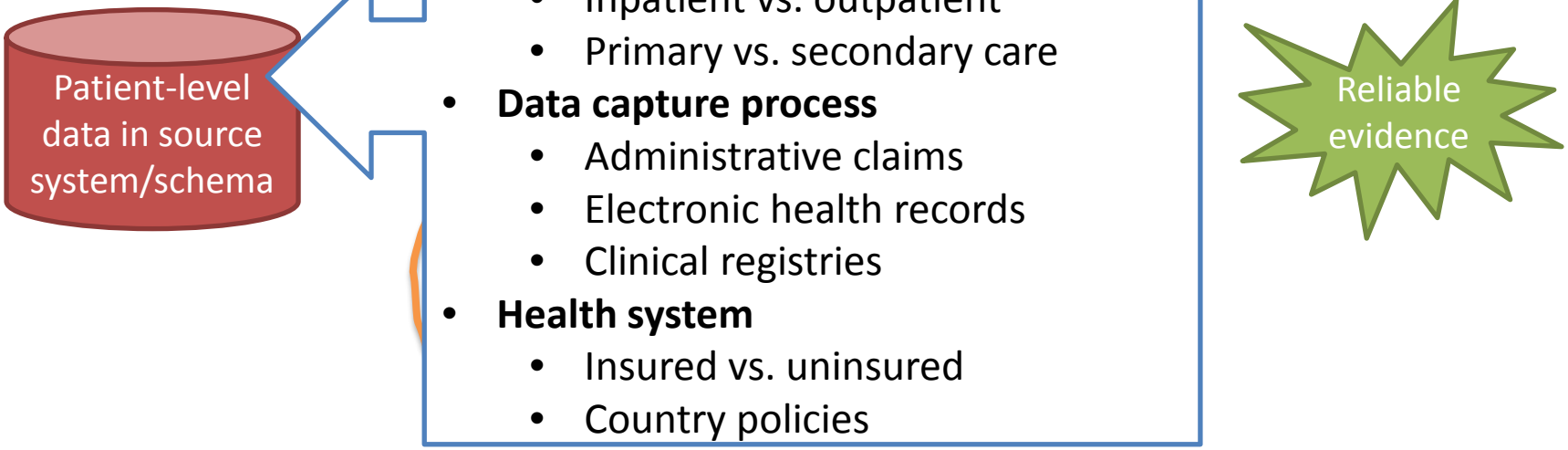
The journey to real-world evidence



One-time

Repeated

The journey to real-world evidence



One-time Repeated

The journey to real-world evidence

Patient-level data in source system/schema

Types of evidence desired:

- **Cohort identification**
  - Clinical trial feasibility and recruitment
- **Clinical characterization**
  - Treatment utilization
  - Disease natural history
  - Quality improvement
- **Population-level effect estimation**
  - Safety surveillance
  - Comparative effectiveness
- **Patient-level prediction**
  - Precision medicine
  - Disease interception

Reliable evidence

One-time

Repeated

Agenda

Day 1

- Group: align on shared problem(s)
- Group photos! 10am
- Break out: design and implement the study
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Day 2

- Group: execute study across data partners
- Group: synthesize results
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F2F objectives

1.Answer a clinical question:

“Predicting randomized clinical trial results with real-world evidence: A case study in the comparative safety of tofacitinib, adalimumab and etanercept in patients with rheumatoid arthritis” Lead: Bridget Wang

2. Learn about improving the real-world evidence generation process:

“It takes a village: An open-science approach to improving the quality and efficiency of the real-world evidence generation process” Lead: Kristin Feeney

Comparative safety of tofacitinib, adalimumab and etanercept in patients with rheumatoid arthritis – Clinical Background and Motivation

Runsheng “Bridget” Wang, MD
Division of Rheumatology, CUMC
Department of Biomedical Informatics, Columbia University

Rheumatoid Arthritis

- A **chronic** inflammatory condition, primarily involving joints.
  - Inflammation in synovium -> pain and swelling of joint
  - Uncontrolled inflammation -> damage in cartilage and bone -> joint damage
- Affecting 1.5 million people in the United States
- Clinical presentation:
  - Chronic joint pain, swelling, morning stiffness
  - Symmetrical, small joints > large joints
  - Extra-articular involvement: rheumatoid nodules, myositis, vasculitis, interstitial lung diseases, pericarditis/myocarditis, scleritis/episcleritis, Sjogren's syndrome, hematologic abnormalities
- Comorbidity and Mortality:
  - Infection
  - Lymphoproliferative disorders
  - Cardiovascular disorders
  - Increased risk for premature mortality
- Diagnosis: Clinical symptoms, blood tests, imaging studies

Management of RA

- Goal of treatment:
  - stop inflammation
  - prevent joint damage
  - improve/reserve physical function
  - reduce long-term complications

Pharmacologic Management of RA

- **D**isease-**M**odifying **A**nti**R**heumatic **D**rugs: DMARDs
  - conventional synthetic DMARDs (csDMARDs) – first line treatment
    - **Methotrexate (MTX),** Sulfasalazine (SSZ), Hydroxychloroquine (HCQ), Leflunomide (LEF), etc.
  - biologic DMARDs (bDMARDs) – infusion or injection
    - TNFi: e.g. **Adalimumab (ADA), Etanercept (ETN),** etc.
    - CTLA antagonist: abatacept (ABT)

Pharmacologic Management of RA

- When patient failed first csDMARDs:
  - Treatment decision is based on:
  - Efficacy
    - No significant difference between bDMARDs vs. tsDMARDs [1,2,3]
      - ORAL Strategy trial: TOF vs. TOF + MTX vs. ADA + MTX
  - Safety
    - Short-term safety data: RCTs
    - Long-term safety data: observational studies, e.g. LTE, registries, cohort studies, etc.

1, Chatzidionysiou et al, 2017
2, Nam et al, 2017
3, Fleischmann et al, 2017

	Tofacitinib (TOF)	Adalimumab (ADA)	Etanercept (ETN)
Mechanism	Jak Kinase inhibitor	TNF monoclonoal Ab	TNF receptor antagonist
Dosage/Route	Oral, 5mg twice a day	SubQ inj, 40mg Q2W	SubQ inj, 50mg QW
Warnings and Precautions	Serious infections	Serious infections Invasive fungal infection HepB reactivation	Serious infections Fungal infection HepB reactivation
	Lymphoma & Malignancy	Lymphoma & malignancy	Lymphoma & malignancy
	GI perferation	Demyelinating diseases	Demyelinating disease
	Lymphopenia, neutropenia, anemia	Cytopenia,	Pancytopenia, aplastic anemia
	Liver enzyme elevation	Heart failure	Heart failure
	Lipid abnormalities	Lupus-like syndrome	Lupus-like syndrome Autoimmune hepatitis

Safety Outcomes

- Infections
  - Serious infections
  - Opportunistic infections: e.g. tuberculosis, herpes zoster
- Malignancies
- Cardiovascular diseases
- Mortalities
- Lab abnormalities: lipid profile, renal function, liver enzymes
- Hematological abnormalities
- GI side effects
- Demyelinating disease
- Induction of autoimmune diseases
- Teratogenicity

Tofacitinib vs. TNFi -

- ORAL Strategy trial[1]:
  - TOF (n=384) vs.
  - TOF + MTX (n=376) vs.
  - TOF + ADA (n=386)

- Efficacy:
  - TOF + MTX was non-inferior to TOF + ADA when assessing ACR50 at 6 months

- Safety:

	Tofacitinib monotherapy (n=384)	Tofacitinib and methotrexate (n=376)	Adalimumab and methotrexate (n=386)
Total number of adverse events*	598	652	620
Patients with adverse events	226 (59%)	231 (61%)	253 (66%)
Patients with treatment-related adverse events	101 (26%)	111 (30%)	133 (35%)
Patients with serious adverse events	35 (9%)	27 (7%)	24 (6%)
Patients discontinuing due to adverse events	23 (6%)	26 (7%)	37 (10%)
Patients with severe adverse events (defined by the investigator)	24 (6%)	17 (5%)	23 (6%)
Deaths†	2 (1%)	0	0
Adverse events of special interest			
Serious infections	6 (2%)	10 (3%)	6 (2%)
Herpes zoster (serious and non-serious)	4 (1%)	8 (2%)	6 (2%)
Herpes zoster (serious and non-serious) in patients who were vaccinated	1/69 (1%)	2/75 (3%)	0/72 (0%)
Opportunistic infections (excluding tuberculosis)	2 (1%)	1 (<1%)	2 (1%)
Tuberculosis	0	2 (1%)	0
MACE (non-fatal)	0	0	2 (1%)
Malignancy (excluding non-melanoma skin cancer)	1 (<1%)	0	0
Non-melanoma skin cancer	2 (1%)	0	1 (<1%)

Data are n, n (%), or n/N (%). MACE=major adverse cardiovascular event (includes non-fatal myocardial infarction, fatal cardiovascular event, and non-fatal cerebrovascular accident). *Patients could have had more than one adverse event. †One patient died of urosepsis; one patient died of atypical pneumonia and respiratory distress syndrome associated with influenza A.

Table 3: **Summary of adverse events, serious adverse events, and discontinuations in the safety analysis set**

1. Fleischmann et al. 2017

Tofacitinib vs. TNFi -

- Observational study[1]:
  - MarketScan database (2011-2014)
    - DMARDs (n=5399) vs.
    - TNFi +/- DMARDs (n=13367) vs.
    - Non-TNFi Biologics +/- DMARDs (n=2902) vs.
    - TOF +/- DMARDs (n=164)
  - Effectiveness – assessed by a claim-based algorithm
    - Overall low
    - TNFi, non-TNFi bio > TOF > DMARDs
  - Safety – Hazards of serious infection were not significantly different

1. Machado et al. 2018

An ongoing Phase 3b/4 study

- Safety Study Of Tofacitinib Versus Tumor Necrosis Factor (TNF) Inhibitor In Subjects With Rheumatoid Arthritis (NCT02092467)
- https://clinicaltrials.gov/ct2/show/NCT02092467?cond=NCT02092467&rank=1
- Study Subjects:
  - I/C:
    - Age > 50 yo
    - moderate to severe RA
    - IR to MTX
    - One CV risk factor
  - E/C:
    - Current or recent infection
    - Clinically significant lab abnormalities
    - pregnancy
- Intervention: TOF 5mg BID vs. TOF 10mg BID vs. ADA or ETN
- Primary Outcomes: malignancy, Incidence of MACE
- Secondary Outcomes: Opportunistic Infections, Hepatic events, CV events other than MACE, all cause mortality, DAS28, ACR20, CDAI, ACR50, ACR70, HAQ-DI

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Group photo!