The SMART pragmatic clinical trial toolbox

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Rationale & hypothesis

Metformin is the current first-line therapy in T2D, but the evidence is weak.

SGLT2 inhibition as add-on to usual diabetes treatment has recently been shown to lower the risks for premature death and cardiovascular events in type 2 diabetes (T2D) patients.

We hypothesize that SGLT2 inhibition will provide at least 20% reduction in total mortality compared to metformin.

The hypothesized result would change the treatment paradigm dramatically, with a shift from metformin to SGLT2 inhibition as first-line therapy, and substantial prolongation of life, particularly in T2D patients with high cardiovascular risk.

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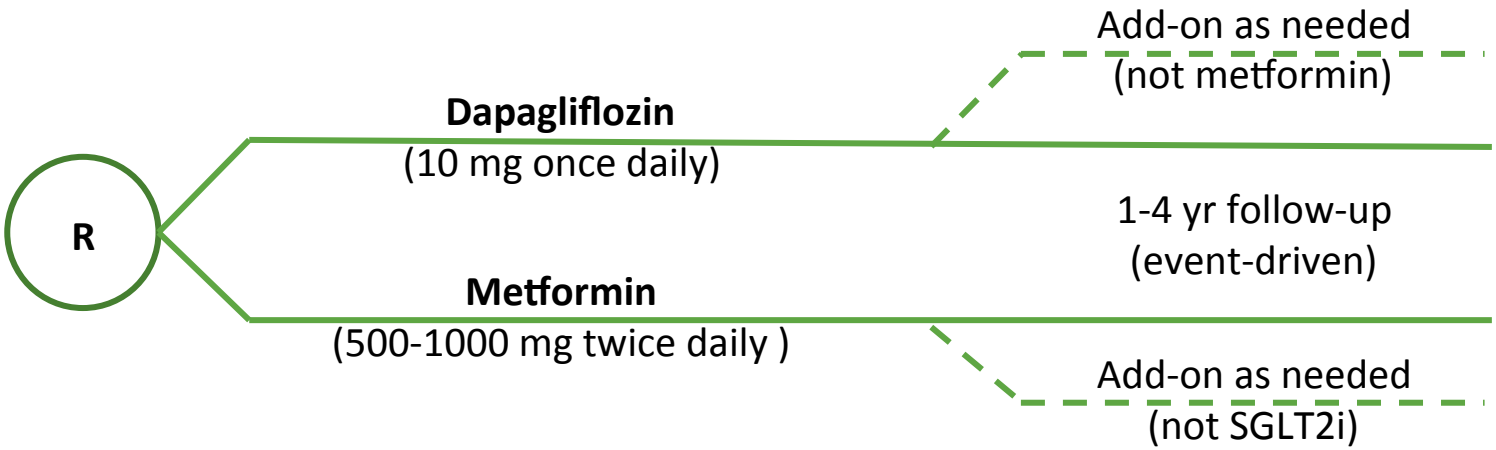
SGLT2 INHIBITOR OR METFORMIN AS STANDARD TREATMENT IN EARLY TYPE-2 DIABETES (SMART)



Patients
N=7,950*, recruited during 3 years
T2D patients, >40 years old
Drug naïve or metformin alone or combined w 1-2 drugs: SU, DPP4i or α-glucosidase-i (no GLP1-RA, insulin or SGLT2i)
60% with established CVD
Recruitment via quality registries (RIKS-HIA, SEPHIA, NDR), primary care, hospital clinics

Primary endpoint
Reduction in total mortality

Secondary endpoints
MACE (MI, UA, stroke, heart failure, or CVD death); individual MACE components
Glucose control (HbA1c, treatment failure, severe hypoglycemia)
Risk factor levels (blood pressure, body weight)
Health-related quality of life, health economy

*90% power for 20% reduction in primary endpoint, two-sided α=0.05

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The need for pragmatic studies

Prospective Registry-based Randomized Clinical Trials (RRCT) is a new opportunity for clinical research

National clinical quality registries are strong networks for collaboration; enrol complete patient populations; collect large numbers of high-quality data and events; inexpensive

"The randomized registry trial represents a disruptive technology, a technology that transforms existing standards, procedures, and cost structures."

Mike Lauer, NIH

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The need for sharper tools

Pragmatic trials need an advanced infrastructure. Sweden has an advantage in this respect due to its abundance of public registries and universal access to healthcare, laying a firm foundation for trials that involve the whole population with maximal access to key data.

Far from all research questions have the luxury of a mature healthcare quality registry to provide cost-effective solutions to the entire infrastructure. Many pieces of the puzzle are lacking for most medical fields, such as primary care-based traits like diabetes.

Hence, more components of the infrastructure for pragmatic trials are needed.

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The ADAPTABLE Aspirin Study

pcornet
The National Patient-Centered Clinical Research Network

A national resource for conducting patient-centered research by harnessing the power of health data.

THE QUESTION

Clinicians often prescribe aspirin to prevent strokes and heart attacks in people living with heart disease. Research has yet to determine the best dose to use, since aspirin can cause serious side effects – like bleeding – in some people.

THE PROBLEM

Heart disease is the No. 1 killer in the U.S.

611,000
people in 2013, one death in 4; accounting for 1 in every 6 healthcare dollars.

Cardiovascular disease (heart attack and stroke) is the most common form of heart disease.

Heart disease strikes someone in the U.S. about once every
43 seconds.

Aspirin is widely prescribed to prevent heart attacks and strokes in people living with heart disease.

60%
of patients with heart disease take a 325 milligram dose each day while 36% take 81 milligrams (or baby aspirin).

THE STUDY

The ADAPTABLE trial will compare two common aspirin dosages.

The study will be large and will involve patients across the U.S.

20,000
patients living with heart disease will use a daily aspirin dose of either 81 mg or 325 mg.

ADAPTABLE will use PCORnet to conduct the study and disseminate results. Patients will be partners at every stage of the trial, which will collect data using tools with state-of-the-art security.

ANSWERS for BETTER CARE

Results of this study will help patients and their caregivers answer questions like:

- **How much aspirin should I take each day to reduce my risk of another heart attack or stroke?**
- **Do the benefits of taking aspirin every day differ based on the dose?**
- **Do the risks differ based on the dose?**
- **Based on my health, age, and other circumstances, what's the best dose to protect my health?**

This study will use the power of PCORnet to seek answers to these questions and improve patient care and outcomes.

DATA — KNOWLEDGE — CARE

Identifying the aspirin dose that works best could prevent as many as 88,800 deaths per year worldwide

pcori

PCORnet is an initiative of the Patient-Centered Outcomes Research Institute.

Deliverable & activities

Main deliverable: **a *complete integrated digital toolbox for pragmatic clinical trials***, including online patient identification, digital informed consent, online randomization, online CRFs that are pre-filled out with EHR data, and a patient-operated smartphone tool for PROMs of quality of life and other symptoms.

Key activities: ***modification, set up, and validation*** of the software suite before the start of the trial, and continuous validation of the suite during the trial. Experienced system architects and quality assurance staff at UCR will conduct the validation of these tools ***for pragmatic clinical trials***, and will monitor the integration from a GCP and ethicolegal perspective.

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Building the pragmatic trial toolbox

Electronic patient identification and case report forms

- MedRave4™, MedRave Software AB

Digital capture of symptoms, side effects, quality of life, and general functions

- Symptoms™, Symptoms Europe AB

Electronic informed consent

- Enroll™, Mytrus
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Web-based randomization

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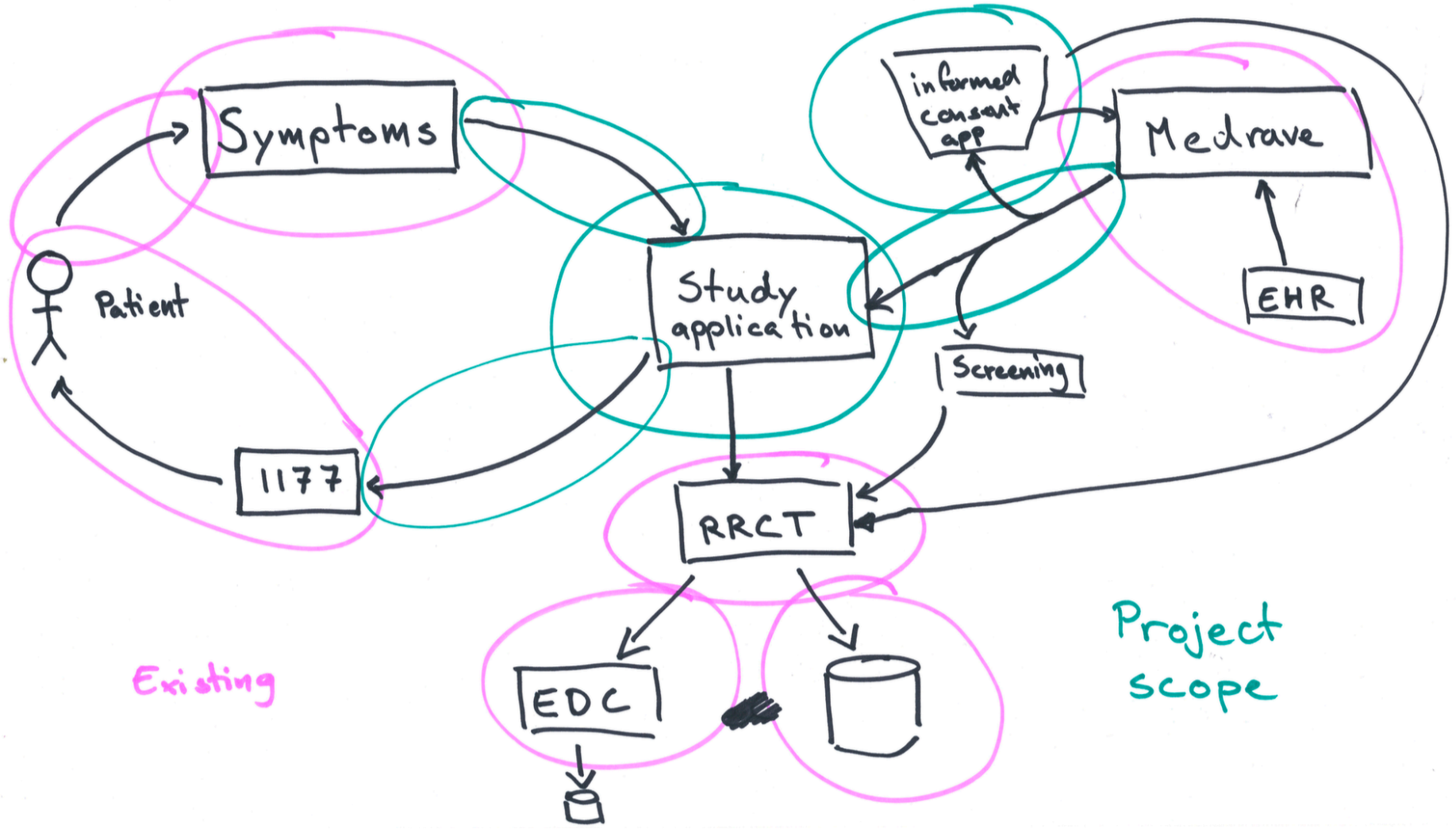
Symptoms
informed consent app
Medrave
Patient
Study application
EHR
Screening
1177
RRCT
EDC
Existing
Project scope

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Uppsala Clinical Research Center

Part of Uppsala University and Uppsala University Hospital.