The Heartline Trial: A Virtual Trial

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Slide by C. Michael Gibson, M.S., M.D.

Old World vs New World: Information Flow

Old World	New World
Insular and Secretive	Open Source
Innovate from within	Innovate from without
Knowledge flowed only to those at the top	Knowledge flows to and from all
Medium: Paper	Medium: Internet
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Gibson CM, JAMA Cardiology 2016

Old World vs New World: Organizations

Old World	New World
Symbol: The silo	Symbol: The Globe
Organization: Vertical	Organization: Horizontal
“Command and Control”	“Cocreation” “Collective genius” “Peering” “Online collectivism”
The corner office	Open space no walls

The Patient Now Has A Seat At The Table

Gibson CM, JAMA Cardiology 2016

Access to Medical Information and a Voice on the Internet has Empowered Patients Lowering Physician / Patient Power Gradient

Old World

Trusted provider conveys paternalistic, proscriptive information to uninformed patient in a one-way conversation

New World

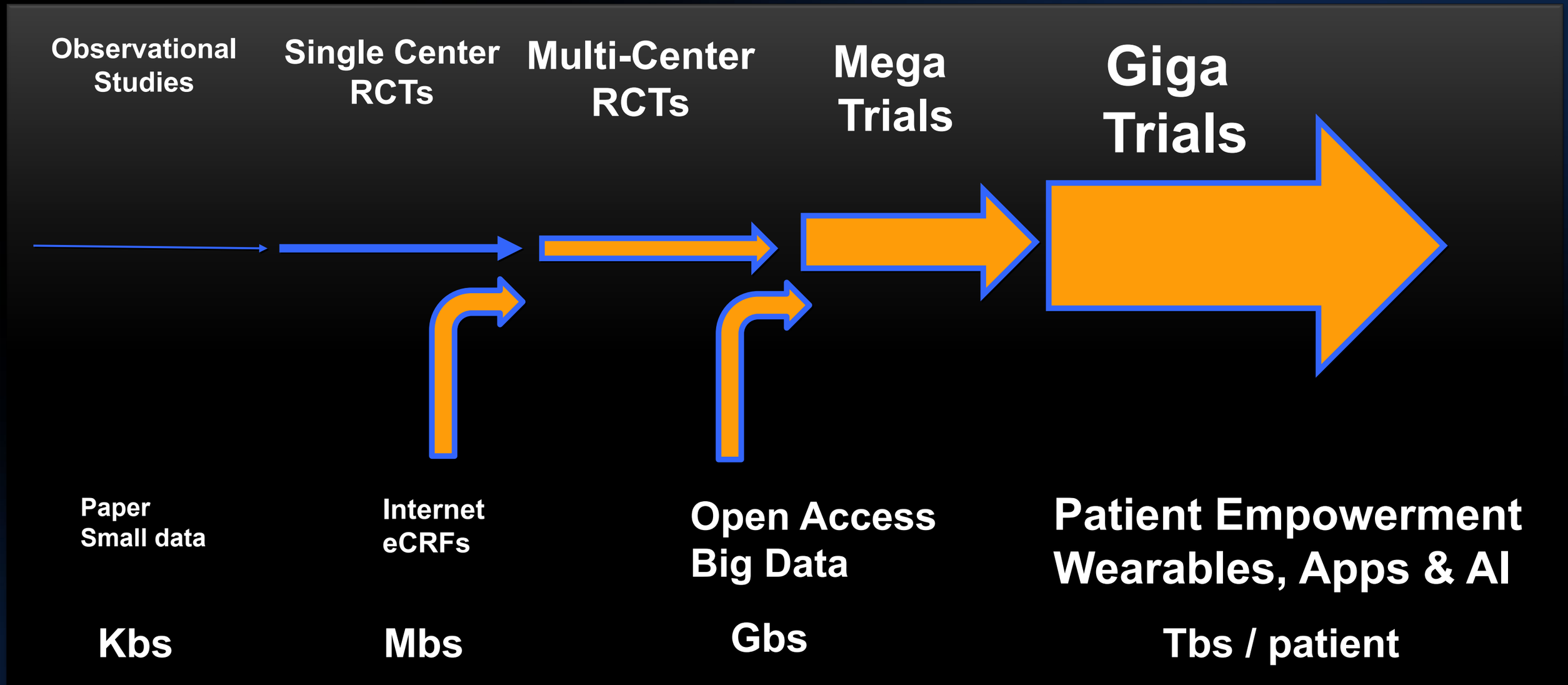
We must now earn the trust of relatively informed & knowledgeable patients through a two-way conversation

Gibson CM, JAMA Cardiology 2016

The Heartline Giga Trial is the Culmination of all These Changes

Open access of patients to participation irrespective of geography and provider
& open access of patients to their data
Social media features: family members alerted to outcomes
Use of electronic health records +
Patient reported outcomes
Patient empowerment &
Patient Compensation
Wearables
Big data
Apps

Evolution of the Giga Trial



The HEARTLINE Trial of the Apple Watch to Detect Atrial Fibrillation in Participants ≥ 65: Entering the Era of the Giga Trial

A randomized trial of up to @ 28,000 patients to test whether the new Apple watch (with a built-in single lead EKG) can detect new onset atrial fibrillation in participants ≥ 65

Does this reduce the risk of all cause death, stoke, MI and CV hospitalization?

This virtual trial will cost 1% of what it costs to do a traditional RCT

Patient Empowered Trials Will Replace Bricks and Mortar

Old World

Hospital Based Trial

Patients enrolled, consented on paper & randomized in hospital or clinic

Patients followed up in hospital or clinic using paper or eCRFs

New World

Virtual Trial

Patients enrolled via app on-line

Patients followed-up on-line by apps for Patient Reported Outcomes (PROs) and claims databases

Consent

Old World

- Paper
- Institution specific
- Local IRB

New World

- Electronic
- Global
- Central IRB

Patient Empowered Trials will Provide More Generalizable Results

Old World

Single center studies, multicenter studies, International **Mega** trials of 10,000 to 20,000 patients

Includes only a ***highly select target population*** with greatest modifiable risk to reduce sample size

Limited generalizability

New World

HEARTLINE is a **Giga** trial of @ 28,000 patients

Includes ***real world patients*** with a broad range of modifiable risk and limited exclusion criteria

Broader generalizability

Ability to Definitively Test Primary Hypothesis

Old World

Possibly *underpowered*

Depending upon event rates, *may not test primary hypothesis definitively*

May not be powered to assess secondary hypotheses

New World

Well *powered*

Definitive test of primary hypothesis

Likely well powered to assess secondary hypotheses

Significance of Results

Old World

If treatment effect robust enough to be statistically significant, generally clinically significant

New World

Trial so large that treatment effect may be statistically significant but not clinically significant

Patient Empowered Trials will Enroll Rapidly

Old World

0.3 (US) to 1.0 (Rest of World) patient per site per month yielding enrollment of **hundreds** of patients per month worldwide

New World

50,000 patients enrolled per month

Direct to Patient Recruitment

- Social Media
- Facebook ads
- Twitter influencers
- At the time of launch interviews with all major print/electronic outlets
- Local TV: 35 local TV & radio interviews in a day
- National TV: Went on “The Talk” to promote the study
- Targeted advertising to demographic group: AARP for instance
- Insurance companies: Not cost effective
- Physicians
- Electronic Health Records

Costs

Old World

$30,000 to $150,000 per patient

Hundreds of millions of dollars per phase 3 pharma trial; sometimes a billion dollars +

Cost to track down missing patients: $50,000 / patient

40% of budget spent on monitoring

New World

Small fraction of cost, @1%

No cost to track down missing patients because claims database is used

No monitoring; automatically drops budget 40%

Patient Empowered Trials: Patient and Family Access to Data

Old World

None during trial, limited access at end of trial

No ability to notify family members of an event

New World

Available on app at all times

Via private social networking family members alerted to event (your family member may have atrial fibrillation)

Specificity and Sensitivity of Endpoints

Old World

Independent physician adjudication of events (Clinical Event Committee or CEC) using rigorous trial specific definitions leads to higher specificity, fewer events

Less sensitive in identifying events

New World

Use of International Classification of Disease (ICD 10 codes, not specific to trial) to find events leads to lower specificity, more events

More sensitive in identifying events

Compliance

Old World

Ideal

Calls from and visits with research team and pill counts improve compliance

New World

Moderate

Approximates real world behavior

Exception is if family members alerted to an event in trial

Adjudication of Events

Old World

Physicians adjudicate each case

Based on evolving definitions that vary across trials (TIMI, BARC, GUSTO, ISTH, Plato bleeding etc)

New World

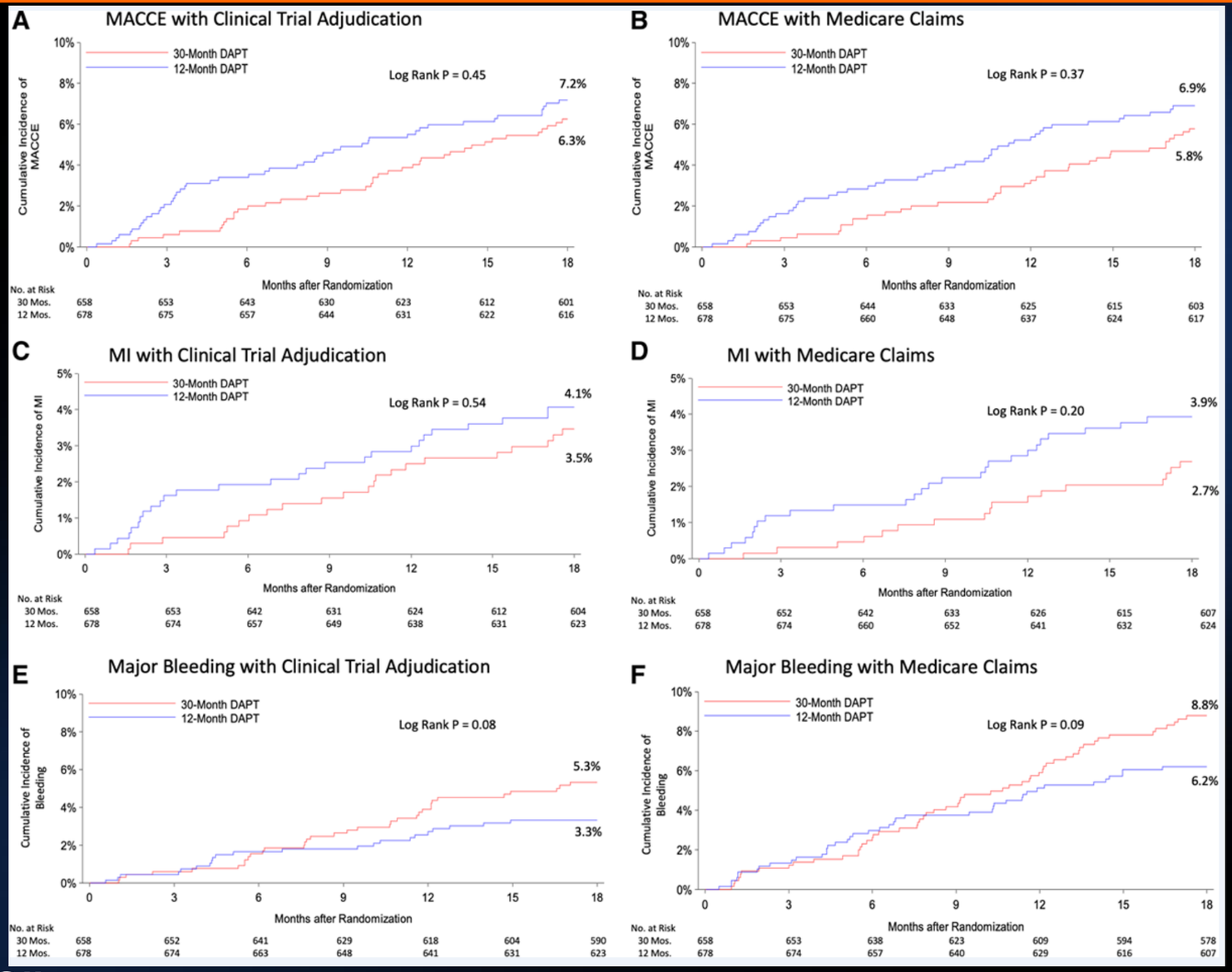
Based on claims data

Worldwide use of ICD 10 codes, peridically updated, single consistent code can be used worldwide

ICD 9 can be translated to ICD 10

CEC vs Claims Database in the DAPT Trial

DAPT Study data linked to the American College of Cardiology's NCDR (National Cardiovascular Data Registry) CathPCI Registry and Medicare fee-for-service claims & CEC c/w claims data



Faridi KF, …Gibson CM, Yeh R. Circulation. 2020;142:306–308

Reimbursement for Labor

Old World

Doctors and Nurses and Hospital reimbursed

New World

Patient reimbursed for effort to complete patient reported outcomes and interacting with App

Safety Monitoring

Old World

Site reports event
Site collect documents
Documents sent to CEC
Documents redacted
Documents translated
Queries issued
Event adjudicated
Additional queries sent
Final adjudication

Delay in updated data for DSMB meetings

New World

Continuous monitoring of ICD 10 diagnoses

Real time data for DSMB meetings as data always caught up (or caught up to the time of discharge or death)

Missing Data

Old World

Missing data may approximate event rates

Risk of informative censoring

Eg: Frail, old people who bleed drop out leaving only young healthy people who passed “bleeding stress test”, lowering the risk of Death / heart attack and stroke in remaining patients

New World

Little to no missing patients (unless patient leaves country in a US only trial)

Big Data / Artificial Intelligence

Old World

Number of patients / events often modest

"Clean data" NOT available in real time for modeling

More covariates

More may not be better or practicable in utilization

Megabytes to Gigabytes of data

New World

Larger number of patients and events

"Clean data" available in real time to guide trial modifications

Fewer covariates though

With wearables can be Terabytes to Pentabytes of data

Patient Empowered Trials Will Yield Patient Specific Predictions

Old World

Guidelines based medicine (one size fits all)

Traditional population statistics

New World

Personalized medicine (tailored to every kind of "ome" & risk factors)

Artificial intelligence to make predictions re individual outcomes

The Appropriate Role of Digital Health

"You can't list your iPhone as your primary-care physician."

Technology should work for healthcare

Healthcare should not work for technology

Health information does not equal healthcare

Digital health should not compete with but should compliment Nurses and Doctors

Putting patients at the center of trials will be the future