University of Barcelona - Faculty of Medicine

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INTERNATIONAL SOCIETY FOR CARDIOVASCULAR INFECTIOUS DISEASES

16TH SYMPOSIUM

ISCVID

Antibiotic prophylaxis of IE: When will we have a clinical trial to clarify our doubts?

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When will we have a clinical trial to clarify our doubts?

SOON!

Soon, hopefully…

Background: Antibiotic prophylaxis of IE

- Animal experimentations showed that AP effectively prevents IE
- Human experimental trials showed that penicillin prophylaxis reduces the incidence of bacteremia after dental extraction
- No RCT has ever been conducted to confirm the efficacy of AP
- Human observational studies
  - The efficacy of AP has been challenged in case-control studies
  - Transient bacteremia is common with normal daily activities such as tooth brushing, flossing and chewing food, which may contribute to the risk of IE at least as much as dental procedures
  - The widespread antibiotic contributes to the emergence of antibiotic resistance
- AP of IE is recommended by expert guidelines
  - except in some countries, due to the absence of evidence of clinical efficacy in humans
  - in France, AP of IE is recommended and implemented in about 50% of IDP

Prophylaxis for infective endocarditis: let's end the debate

Published Online
November 18, 2014
http://dx.doi.org/10.1016/
S0140-6736(14)62121-8

Despite continued progress in the diagnosis and treatment of infective endocarditis, in-hospital mortality associated with this disease remains at about

by oral streptococci. One of these studies[8] was done in the UK and analysed the 3 year period after the NICE guidelines were issued.

- 1992: "the doctrine of faith, hope, and charity may be a philosophy for life: it is no basis for perpetuating costly and possibly ineffective medical practices" : prospective randomised controlled studies to assess the efficacy of antibiotic prophylaxis in infective endocarditis should be performed in a European collaborative effort (Lancet editorial)
- More than 20 years later, no such study has been done
- 2015: "We strongly suggest that experts stop elaborating guidelines for infective endocarditis prophylaxis, and urgently join forces to mount an international collaboration to do the appropriate clinical trials that are needed to answer this important question" (Lancet editorial)

Duval X, Hoen B. Lancet 2015;385(9974):1164-5

Dublin 2017

14th International Symposium on

Modern Concepts in Endocarditis and Cardiovascular Infections

Pre-ISCVID workshop on

"Planning a randomized clinical trial in prophylaxis of IE"

June 22, 2017, 8am – 12pm

François Alla, Mark Dayer, David Durack, Xavier Duval, Bruno Hoen, Peter Lockhart, Bernard Prendergast, Martin Thornhill

The APPROVED clinical trial

- Assessment: a good study design with high chance of delivering a clear outcome
- Estimate: 2 years - set up/approvals, publicise etc. 5 years data collection, 1 year analysis (Total 8 years)
- NIH priced study at US$60m (Euro 53m, £38m) i.e. x3
- About to consider funding when 2012 'Fiscal Cliff' financial crisis hit USA
- NIH required to stop all new funding
- 2013 – NIH Funding freeze lifted
- Politically US$60m now considered too high a cost for any RCT – particularly when entirely outside USA

The Randomized Registry Trial — The Next Disruptive Technology in Clinical Research?

Michael S. Lauer, M.D., and Ralph B. D'Agostino, Sr., Ph.D.

N ENGL J MED 369;17 NEJM.ORG OCTOBER 24, 2013

Rationale for a registry-based RCT

- On the one hand, conducting a conventional individual-based RCT to demonstrate the efficacy of AP of IE is unfeasible and unethical, especially as AP is currently recommended in France
- On the other hand, it is unacceptable to perpetuate potentially ineffective, hazardous and ecologically deleterious practices
- To solve this catch-22 situation, we started thinking of a registry-based RCT with the objective to demonstrate the effectiveness of AP of IE after invasive dental procedures in high-risk patients

What is a randomized registry-based trial?

- A registry-based trial is a RCT conducted within or with the help of a registry or multiple registries, the registries being used to
  - identify patients
  - replace the CRF
  - carry out patients' follow-up
- R-B RCTs have already been conducted
  - TASTE (Thrombus Aspiration during ST-segment Elevation
    - One single registry, 3 countries (Sweden, Denmark, Iceland)
    - PCI + TA vs PCI alone in Patients with ST-segment elevation AM
    - Outcome 30-day mortality
  - CHAP (Cardiovascular Health Awareness Program)
    - 9 registries in a single country (Canada)
    - CHAP vs SOC in community residents aged ≥65 years old
    - Outcome: admission to hospital for AMI, stroke or CHF
  - REDUCE MRSA (Randomized Evaluation of Decolonization versus Universal Clearance to Eliminate MRSA)
    - The corporate data warehouses in the USA (74,256 patients in
    - Universal or targeted decolonization vs isolation in patients ac ons
    - Outcome: rates of MRSA clinical isolates and bloodstream infections

The NEW ENGLAND JOURNAL of MEDICINE

BMJ

The NEW ENGLAND JOURNAL of MEDICINE

Advantages of a R-B RCT? 1. Lower costs

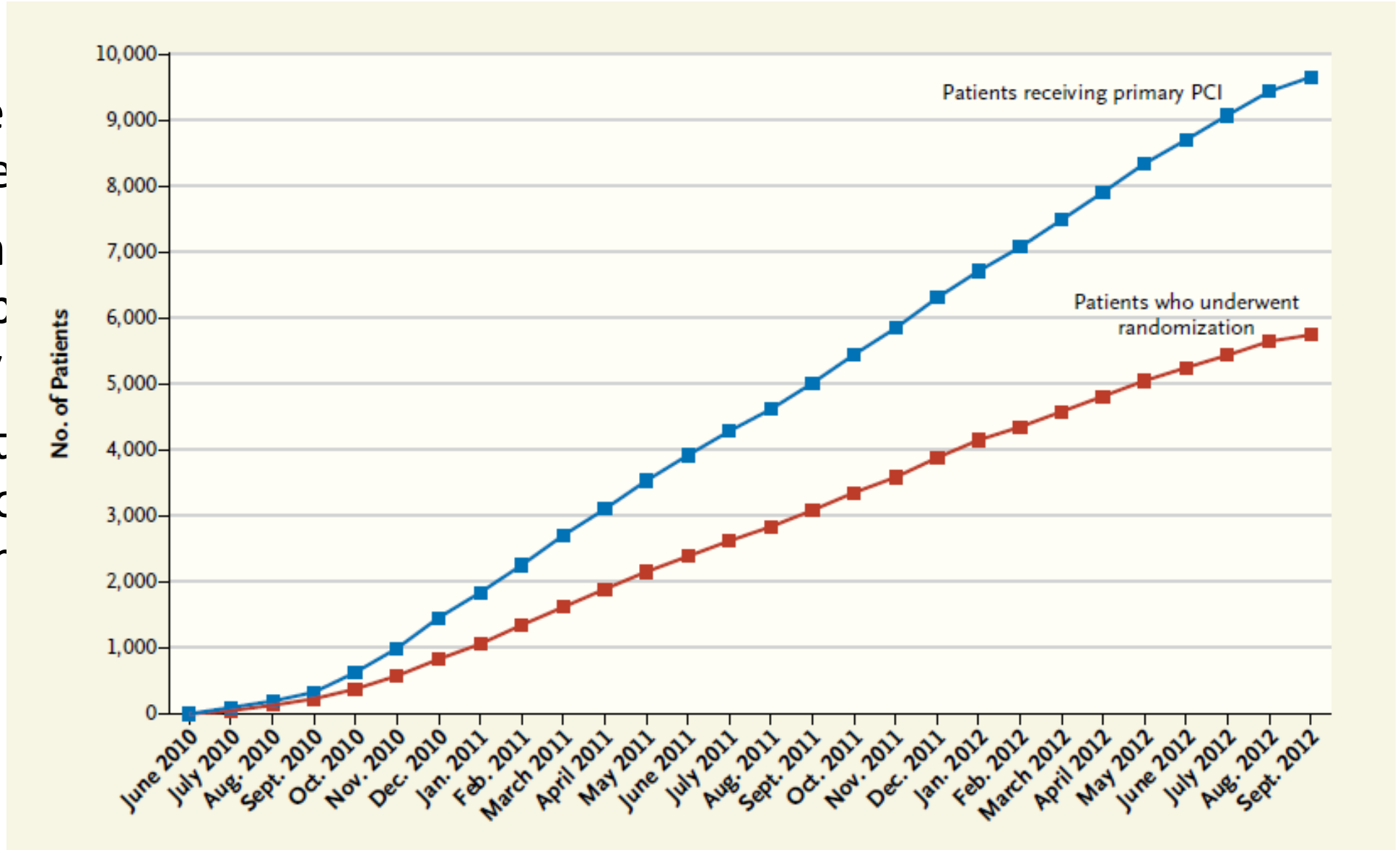
- Examples
  - TASTE 50 USD/patient (300,000 USD for 7,200 pts, 2% of a conventional RCT)
  - CHAP 16 USD/resident (most explanatory trials in CVD cost 5,000 USD /patient)
  - REDUCE MRSA 40 USD/patient
- How can this be achieved?
  - use of existing registries to
    - identify participants
    - collect baseline and study data
    - detect outcomes
  - (Costs that would normally be incurred in a more traditional randomized controlled trial are indirectly transferred onto the health system where electronic registries are maintained)
  - Reduced or even no cost of follow-up study visits
  - Minimization of extra administrative costs
  - Cost saving in training site staff and research coordinators
  - For example, in the TASTE trial, the trial did not
    - create any additional case report forms for data collection
    - require any additional patient visits
    - organize training sessions for trialists and staff

Advantages of a R-B RCT?
2. Enhanced generalizability of findings

- Generally, in R-B RCTs
  - Inclusion and/or exclusion criteria are less stringent
  - Patient monitoring and follow-up are more akin to real world than the more intensive monitoring in explanatory trials, which enhances the generalizability of their findings
- The cost and recruitment efficiencies of R-B RCTs are most times fully realized with trial designs that allow recruitment of less-selected populations in real-world settings, where blinding or crossover prohibitions are not required, and where follow-up end points can be abstracted from other registries or health care administrative data
- Consequently, findings from well designed registry-based randomized controlled trials may be broadly generalizable while answering a comparative effectiveness research question

Advantages of a R-B RCT?
3. Rapid consecutive enrollment

- In R-B RCTs, inve
  rapidly identify e
- They may no lon
  participant eligib
  registry, thereby
- For instance, in t
  segment elevatic
  within 2 years ar



Advantages of a R-B RCT?
4. Potential completeness of follow-up

- In countries where unique patient identification numbers in registries are available (Nordic European countries, Canada, France, India), these allow for an almost complete tracking of patients across registries
- Because of the linkage to registries such as interconnected health records, it is possible to retrieve extensive clinical information of participants using their unique identification number in the tracking system
- R-B RCTs have the potential to describe and follow up the complete reference population for
  - eligible but nonrandomized participants
  - noneligible participants

R-B RCTs: limitations and challenges
1. Registry data quality

- Definition, collection, and accuracy of baseline data gathered in registries may be various and questionable in terms of quality
- Outcome data documented in registries may be subject to uncertainty
- Registries may have many missing data or fail to capture important prognostic factors

R-B RCTs: limitations and challenges
2. Ethical issues

- Screening registry participants for trial inclusion if they have not previously consented to records review
- The potential need for formal informed consent for a treatment that is already being used in routine practice
- Protecting the data and participant privacy
- How to handle participant withdrawal from the trial or registry
- How to coordinate the overlapping role of Data and Safety Monitoring Board in the trial with the role of registry executives

R-B RCTs: limitations and challenges
3. Methodological issues

- Common confusion and controversies about the research question being addressed by the study design
- Ensuring the representativeness of study participants in recruitment
- Research questions, study designs, and types of outcomes limited by quality and features of registries to be used
- Guidelines for reporting study results are still to be written
- Criteria analogous to those of GRADE system for R-B RCTs are still lacking

How could a registry-based randomized trial be implemented for assessing effectiveness of AP of IE?

How could a registry-based randomized trial be implemented for AP of IE?

- Population (registry-based)
  - Registries make it possible to identify (all) people with high-risk conditions (prosthetic valve, other…)
- Randomization (not registry-based but cluster-based)
  - Geographic area
  - Dentist's patients
- Follow-up and Endpoint (registry-based)
  - National hospital discharge diagnosis database
  - Advantage
    - virtually all IE cases are diagnosed and treated in hospitals
  - Drawbacks
    - Diagnosis of IE may not be expert-validated
    - Causative microorganism may not be reported

How could a registry-based randomized trial be implemented for Abpro of IE? Situation in France (1)

- The French National Health Insurance information system (SNIIRAM), anonymously collects all individual and health care claims reimbursed by the French National Health Insurance (covering the whole French population). It is linked/merged with the French Hospital Discharge database (PMSI), which contains discharge diagnoses (ICD-10 codes) and medical procedures for all patients admitted to hospital in France
- From this database it would be possible to
  - set up a cohort of patients with prosthetic valves and/or prior IE
  - observe and define a target dental intervention during follow-up
  - whether or not antibiotic prophylaxis would be used for this target intervention (whatever the randomization arm),
  - Identify the occurrence of an IE and compare incidence of IE between groups

How could a registry-based randomized trial be implemented for Abpro of IE? Situation in France (2)

- Preliminary analyses from SNIIRAM database (BMJ 2017)
  - 160,000 patients with prosthetic valves (200,000 expected by 2020)
  - Over a two-year period:
    - 94,000 dental interventions
    - 450 IE following these interventions
  - Rate of Abpro in PV carriers (in whom Abpro is recommended): 45%
  - Risk of IE after invasive dental prodedure
    - with Abpro 78/100 000
    - w/o Abpro 150/100 000
- Possible study design (in countries where Abpro is recommended)
  - Intervention: Actions to enforce Abpro according to existing guidelines (objective: reach ≥80% Abpro coverage rate)
  - Control: no intervention (i.e. expected Abpro coverage rate < 50%)
  - Randomization by cluster: geographical area (Territoire de santé)
  - Type of dental intervention: only high-risk
  - Type of at-risk patients: only high-risk (patients with prosthetic valve)

PROPHETS: Effectiveness of antibiotic PROPHylaxis of infective Endocarditis before invasive dental procedures in high-risk patienTS: a registry-based, cluster-randomized trial in primary care

Co-investigators

François Alla, Xavier Duval, Bruno Hoen

Funding
French MoH (DGOS)
PHRC 2021

Main objective

- To evaluate the effectiveness of antibiotic prophylaxis before invasive dental procedures to prevent oral streptococcal infective endocarditis within 3 months of the invasive dental procedure in patients with prosthetic heart valves and/or history of endocarditis, using a registry-based cluster-randomized controlled trial

Secondary objectives

- Analysis of changes in dentists' practices
  - Practices will be continuously monitored during the study to assess the impact of the intervention on dentists regarding deliveries of antibiotic prophylaxis (both adequate and inadequate) in patients with and without PHV/PHIE
- Safety monitoring
  - Although this trial aims directly dentists' practices, we will also monitor adverse events of antibiotic prophylaxis
  - To describe the safety of antibiotic prophylaxis in patients with PHV/PHIE regarding the risk of severe anaphylaxis

Study Population

- **Main inclusion criteria**
  - All French “territoires de santé” (TDS, a health territory) will be included and each TDS will contribute as a cluster for randomization. All dentists working in TDS will be included
  - The study population will be identified in the SNIIRAM database
  - Among individuals receiving an invasive dental procedure, all patients aged 18 years or more identified with prosthetic heart valves (PHV) or with prior history of IE (PHIE) will be included
- **Main exclusion criteria**
  - There will be no exclusion criteria for health territories, dentists and patient
  - We will not include dental procedures that had been performed less than 6 months after the date of first implantation of PHV

Randomization clusters

- Intervention cluster
  - All the dentists working in a cluster randomized to the intervention arm will be provided with an AP package aimed to improve adherence to AP guidelines for IDP in patients with PHV
- Control cluster
  - In the cluster randomized to the control arm, no intervention will be performed and no information will be sent to dentists

Endpoints

- Primary endpoint
  - Incidence of infective endocarditis due to oral streptococci within 3 months after an invasive dental procedure is performed
- Secondary endpoints
  - Analysis of changes in dentists' practices
    - We will calculate antibiotic prophylaxis rate in dentists according to their randomization arm (Health territories) taking into account the type of patients (w vs w/o PHV/PHIE) and the nature of dental procedures (invasive or not)
  - Safety monitoring
    - Description the number of anaphylaxis and immediate death after procedures with any exposure to antibiotic prophylaxis

Number of invasive dental procedures needed

- Considering an incidence of IE of 89.0/100,000 in the intervention arm *vs.* 118/100,000 in the control arm (RR=0.75), α=0.05, 1-ß=0.8, and a coefficient of variation of 0.025, a total of 3,579 IDPs in patients with PHV are needed in 102 clusters (51 vs. 51), i.e. a total of 365,058 IDPs
- The average annual number of IDP/patient with PHV/PHIE is 0.4
- In order to reach the required number of invasive dental procedures, the follow-up period should last 3 years

Methods

- 2-arm, registry-based, cluster RCT
  - to be conducted in all French Health Territories (Territoires de santé, TDS), which will serve as randomization clusters
  - All dentists of the same cluster will either be in the intervention arm or the control arm.
- In the intervention arm, dentists will receive information on the study 8 weeks before the start of the study and will be invited to consent to participate or to opt out. Those who do not opt out will be provided with an "AP package" consisting of
  - user-friendly guideline reminders
  - periodic study reminders
  - communication materials to be posted in waiting rooms (posters, flyers targeting PHV patients)
  - links to specific web pages that will display practical information on AP targeting both dentists and PHV patients
  - e-learning and MOOC training sessions for dentists' secretaries and assistants
  - …
- In the control arm, no intervention will be performed and no information will be sent to dentists

Final answer to the question: 2026

	2021	2022	2023	2024	2025	2026
Pilot study	Nov. →	Aug.				
Intervention development	Nov. →	Oct.				
Ethical and regulatory procedures	Dec. →	Aug.				
Cohort construction, development of algorithms		May. Sep.				
Intervention implementation		Sep. Dec.				
Cohort follow-up			Jan. →			
Analyses					→	
Report and publication						→

“Do what you can, with what you have, where you are.” Theodore Roosevelt

- The randomized registry trial represents a disruptive technology that will transform existing standards, procedures, and cost structures
- Will it be given serious consideration as a way to resolve the recognized limitations of current clinical-trial design?
- Today we can no longer afford to undertake randomized effectiveness trials that cost tens or hundreds of millions of dollars
- But today we have registries and other powerful digital platforms
- Today we must design and conduct megatrials with what we have: bigger data and smaller budgets

Adapted from Lauer and D'Agostino, NEJM 2103;369:1579)

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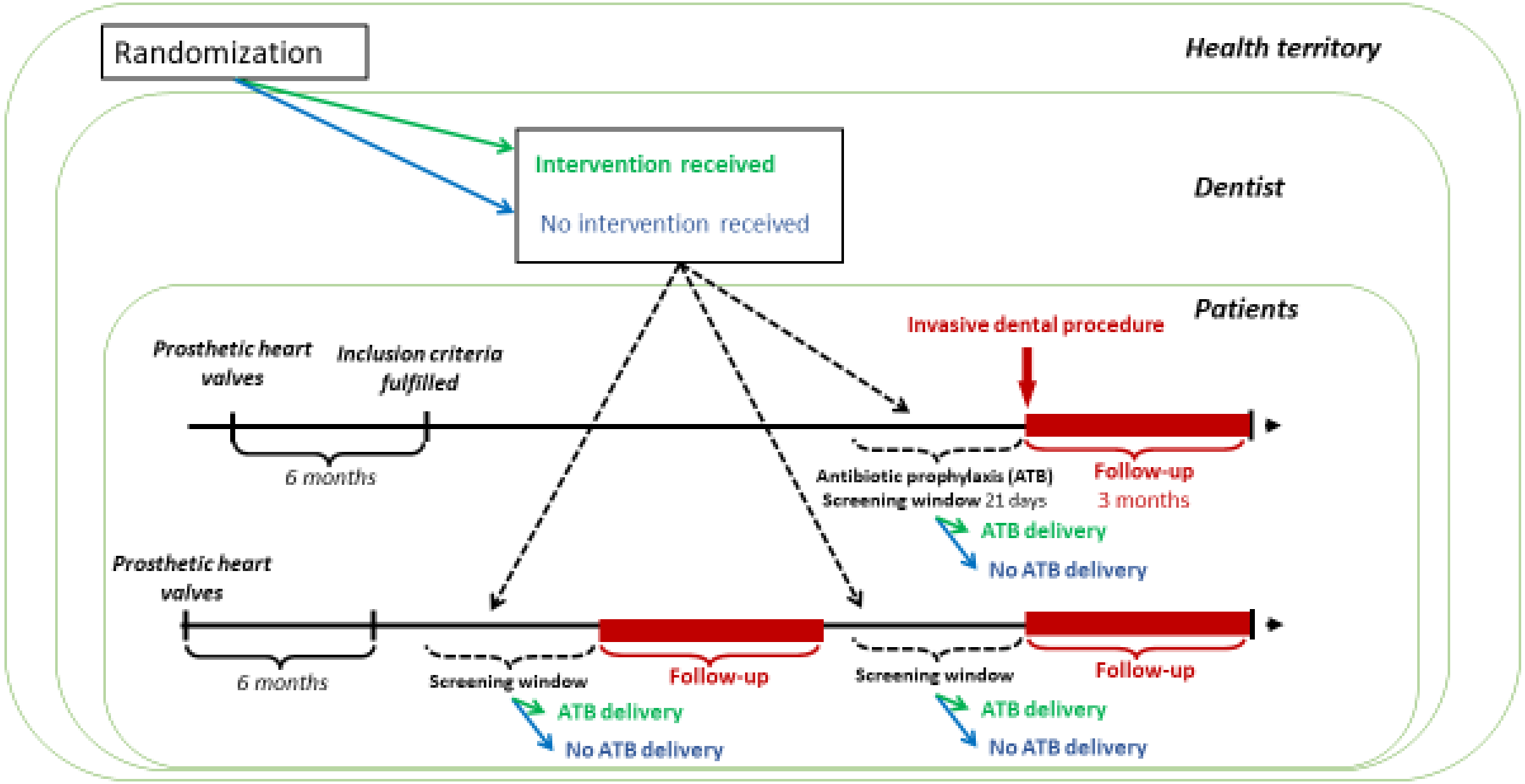
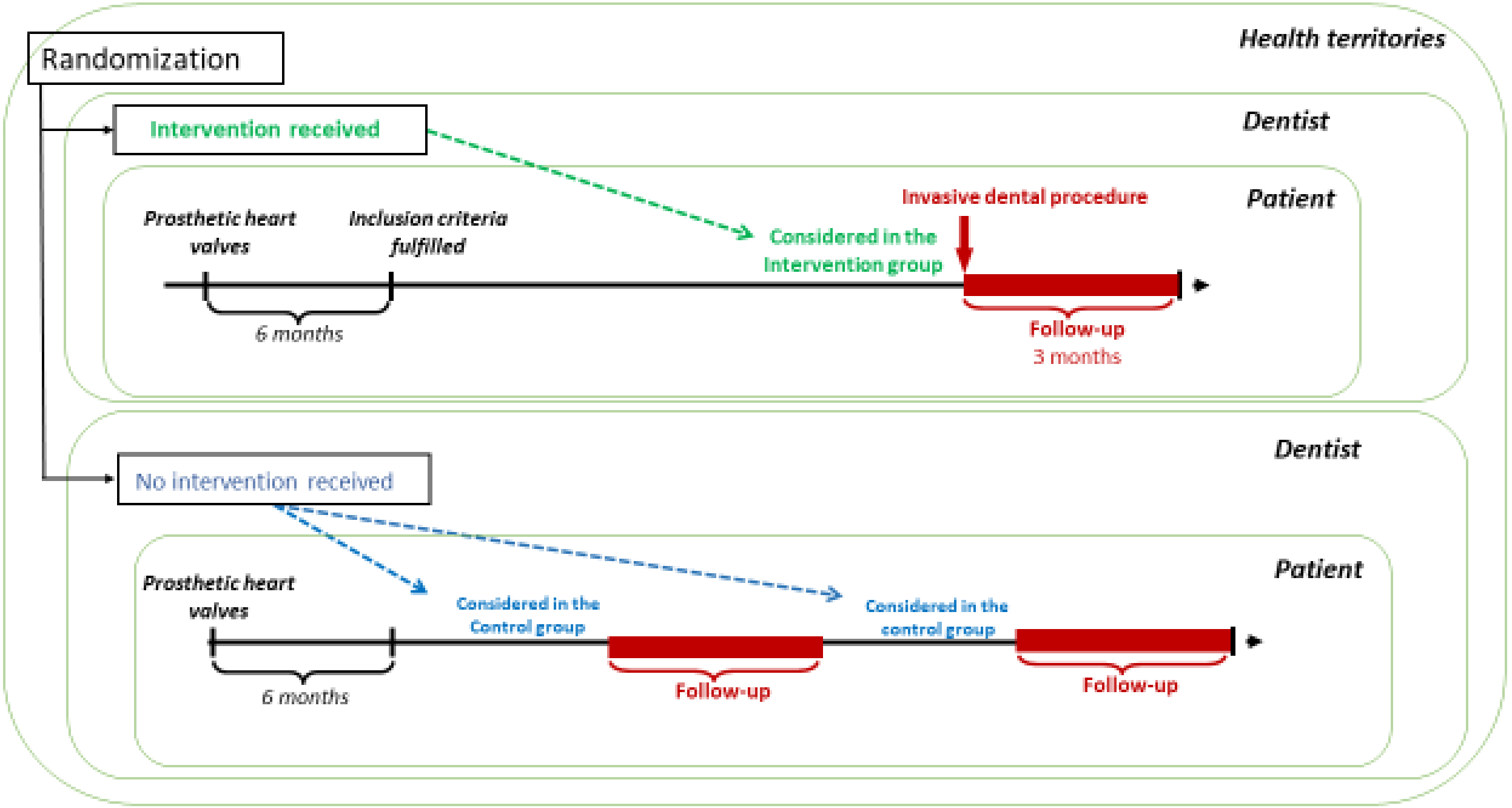
- WP
  - WP1 governance, lead: François Alla, Xavier Duval, Bruno Hoen
  - WP2 intervention, lead: Philippe Lesclous, Sarah Millot, Benoit Perrier, Bernard Iung, Christine Selton, François Delahaye
  - WP3 data management and analyses, lead: Alain Weill, Mahmoud Zureik, Sarah Tubiana Michaël Schwarzinger, Jordan Guillot



Registry randomized clinical trial (RRCT)



Intention-to-treat analysis (ITT)