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# Effectiveness of antibiotic prophylaxis of infective endocarditis before invasive dental procedures in patients at high risk of IE: a registry-based, cluster-randomized trial in primary care

*Efficacité de l'antibioprophylaxie de l'endocardite infectieuse chez des sujets à haut risque d'EI : essai randomisé en cluster sur registre en soins primaires*

***PROPHETS Study (PHRC 2021)***

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# 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 implemented in about 50% of invasive dental procedures

# 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 propose to conduct a RB RCT with the objective to demonstrate the effectiveness of AP of IE after invasive dental procedures in high-risk patients

# Primary objective and endpoint of PROPHETS

- **Objective:** To evaluate the effectiveness of antibiotic prophylaxis before invasive dental procedures to prevent oral streptococcal IE within 3 months of the dental procedure in patients with prosthetic heart valves and/or history of endocarditis, using a registry-based cluster-randomized controlled trial
- **Endpoint:** Incidence of IE due to oral streptococci within 3 months after an invasive dental procedure is performed

# Study population – eligibility criteria

- **Main inclusion criteria**
  - All French “territoires de santé” (TDS, a health territory) will be included and each TDS will contribute as a randomization cluster. All dentists working in each 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**
  - 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

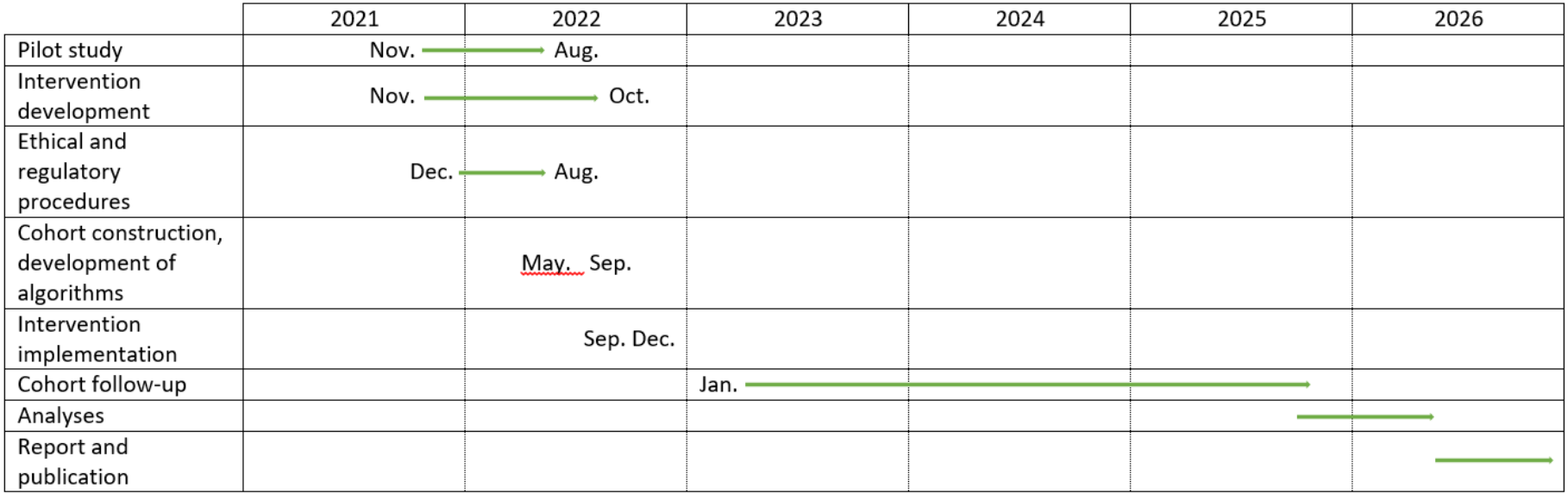
# Methods

- 2-arm, registry-based, cluster RCT
  - conducted in all French TDS, which will serve as randomization clusters
  - All dentists of the same cluster will either be in the intervention or control arm
- In the intervention clusters, dentists will receive information on 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 clusters, no intervention will be performed, and no information will be sent to dentists

# 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

# Research Calendar



# “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