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PIRATE

The PIRATE PROJECT: a Point-of-care, Informatics-based Randomized, controlled trial for decreasing over-utilization of Antibiotic ThErapy in Gram-negative Bacteremia

LARE
Bayerische Landesarbeitsgemeinschaft Resistente Erreger

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Université de Genève

Hôpitaux Universitaires Genève
L'ESSENTIEL, C'EST VOUS.

Outline

- Finding the evidence to support a reduction in antimicrobial usage
  - Point-of-care (POC) randomization trials
    - Learning healthcare systems

- The PIRATE project
  - Antibiotic resistance & what we should learn from our patients
  - Randomization at the point of care for determining optimal antibiotic durations for Gram-negative bacteremia
  - Substudies

PIRATE PROJECT

When the drugs don't work

because we overused them

because we lacked evidence

to show that less usage is OK


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24 January 2013 Last updated at 13:18

Antibiotic 'apocalypse' warning

By James Gallagher

Health and science reporter, BBC News

The rise in drug resistant infections is comparable to the threat of global warming, according to the chief medical officer for England.

Prof Dame Sally Davies said bacteria were becoming resistant to current drugs and there were few antibiotics to replace them.

She told a committee of MPs that going for a routine operation could become deadly due to the threat of infection.

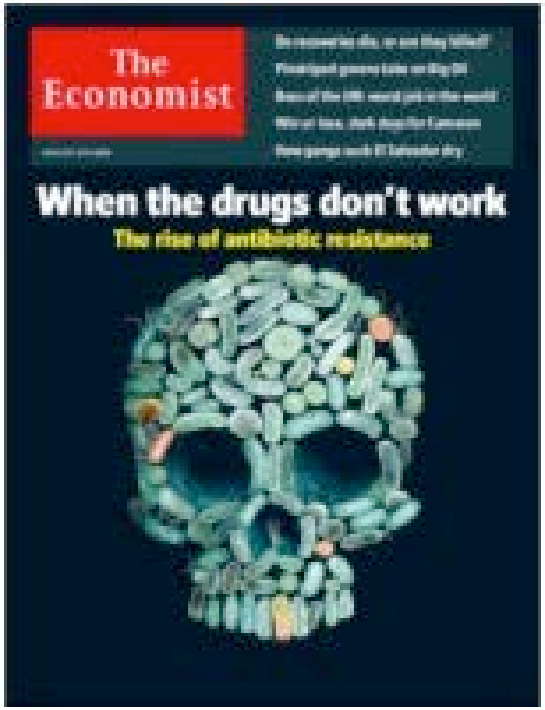
Drug resistance is a problem in tuberculosis

Experts said it was a global problem and needed much more attention.

Antibiotics have been one of the greatest success stories in medicine.

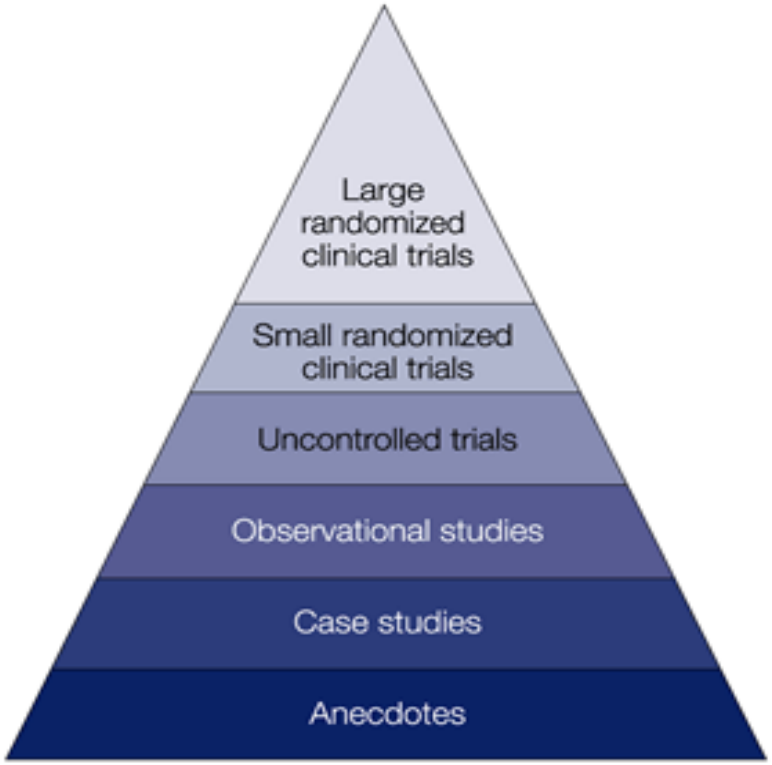
Related Stories

Warning on antibiotic resistance



Point-of-care randomization studies

- Hierarchy of evidence



Engel et al. *Nat Rev Drug Discov* 2002; 1(3): 229-37).

- We don't have enough randomized controlled trials in infectious diseases (only 16% of IDSA recommendations based on them)
- And even randomized controlled trials may lack external validity…
- Spontaneous randomizations occur daily in the clinic, but this "evidence" goes uncollected (anecdotes)

Khan et al. Clin Infect Dis 2010; 51(10): 1147-56

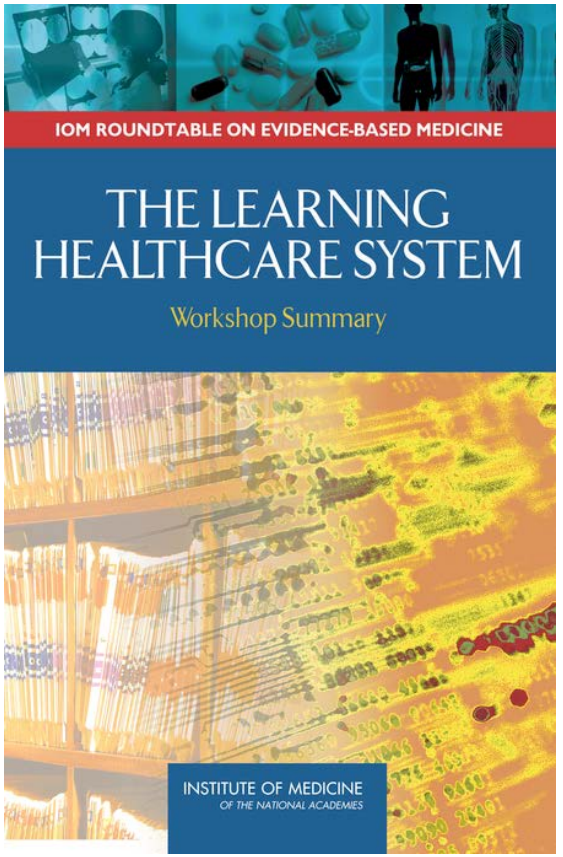
Point-of-care randomization studies

- Use the electronic health record (EHR) to structure spontaneous “pseudo-randomizations” at the point of care
- Enable the coherent study of patient outcomes
  - Data from “real” patients
  - Follow-up visits integrated into usual care
- Clinical evidence can come only from the clinic
- Only suitable for comparing **approved** treatments or diagnostic techniques toward which there is clinical equipoise

Learning healthcare systems

- Institute of Medicine (National Academy of Sciences), 2007 :

A learning healthcare system is…designed to generate and apply the best evidence for the collaborative healthcare choices of each patient and provider; to drive the process of discovery as a natural outgrowth of patient care; and to ensure innovation, quality, safety, and value in health care.



https://www.nap.edu/

Common Purpose principles of learning healthcare systems

1. Respect the rights and dignity of patients
2. Respect the clinical judgments of clinicians
3. Provide optimal care to each patient
4. Avoid imposing nonclinical risks and burdens on patients
5. Reduce health inequalities among populations
6. Conduct activities that foster learning from clinical care and clinical information
7. Contribute to the common purpose of improving the quality and value of clinical care and health care systems

Point-of-care randomization

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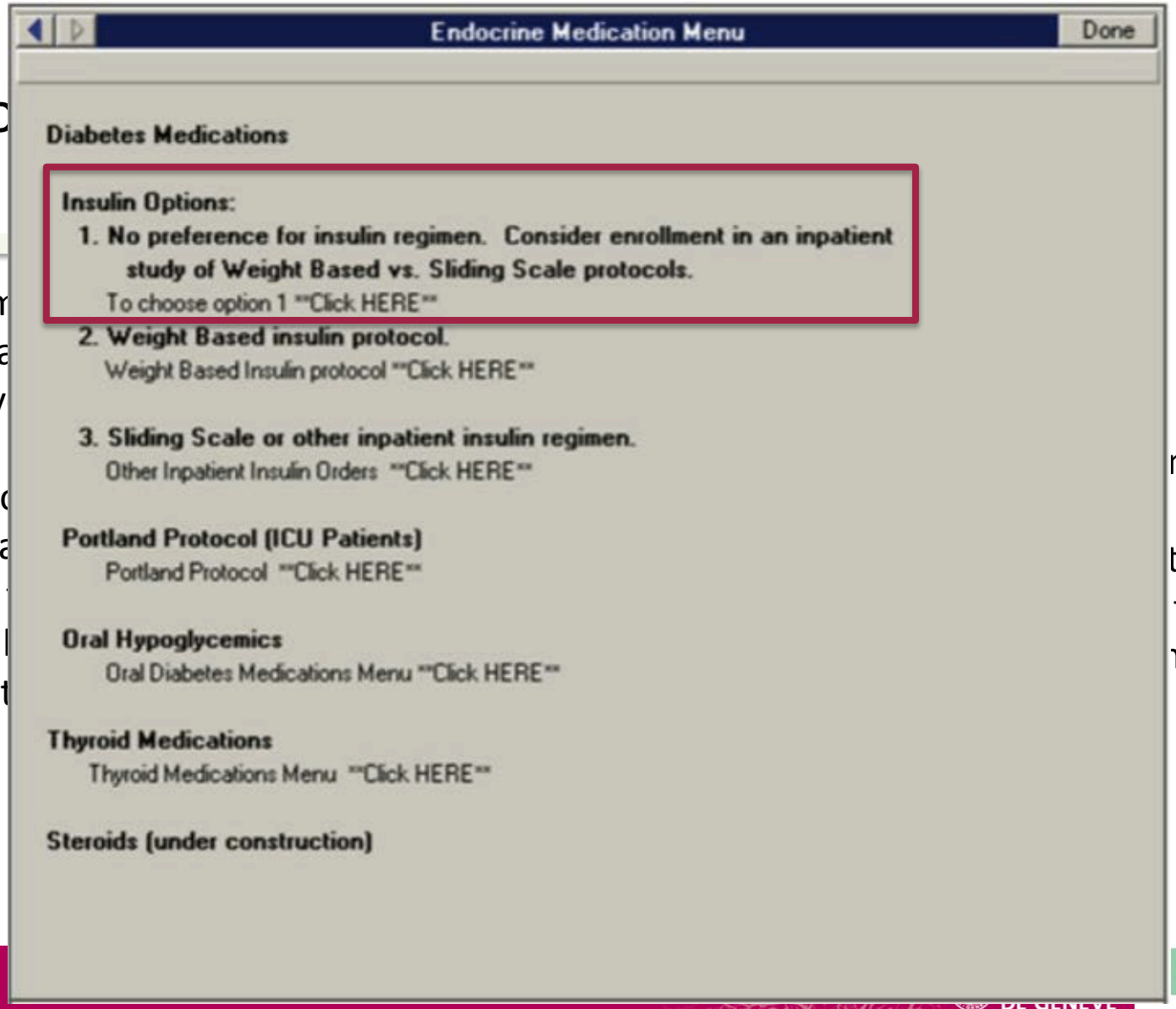

Establishing a point-of-care randomization platform in Switzerland

Box 2
Hypothetical examples of point-of-care trials in infectious disease

- Duration studies: optimal duration of antibiotic therapy for (a) community-acquired pneumonia, (b) uncomplicated pyelonephritis, (c) Gram-negative bacteraemia; early switch to oral antibiotic therapy; etc.
- Antibiotic choice studies: linezolid vs. vancomycin for skin and soft tissue infections; fosfomycin vs. ciprofloxacin for prophylaxis before transrectal prostate biopsy; cloxacillin vs. cefazolin for MSSA bacteraemia; combination vs. monotherapy for carbapenem-resistant, Gram-negative infections; β-lactam monotherapy vs. β-lactam/aminoglycoside for *Pseudomonas aeruginosa* bacteraemia; etc.
- Dosing and schedule: meropenem 1 g three times a day vs. 2 g three times a day; intermittent vs. continuous infusion of antibiotics; pharmacokinetic studies in which no more than routine blood sampling is needed; etc.

MSSA, methicillin-susceptible *Staphylococcus aureus*.

Huttner A, Leibovici L et al. Closing the evidence gap in infectious disease: point-of-care randomization and informed consent. Clin Microbiol Inf 2016

Establishing a point-of-care randomization platform in Switzerland

- Help from above

FNSNF Swiss National Science Foundation

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- A convincing & “easy” first test case, with plenty of safety valves…

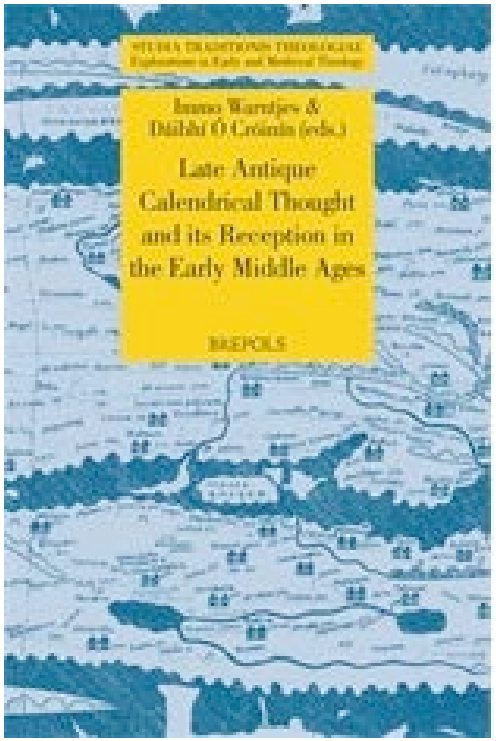
PIRATE PROJECT

The PIRATE project: a Point-of-care, Informatics-based Randomised, controlled trial for decreasing over-utilisation of Antibiotic Therapy in Elderly and comorbid populations

Study question of the platform’s prototype trial:
Are shorter antibiotic courses non-inferior to 14 day courses for Gram-negative bacteremia?

Rationale for the PIRATE project

- We know we overuse antibiotics
- We know that this overuse leaves patients with resistant organisms
- Antibiotic durations are arbitrary…and lunar!
- But physicians are generally afraid to shorten durations without solid (randomized) evidence



Holmes AH et al. *Lancet.* 2015; Bell BG et al. *BMC Infect Dis.* 2014;14:13;
Zarkotou O et al. *Clin Microbiol Infect.* 2011;17(12):1798-1803.

Are shorter antibiotic courses non-inferior to 14 day courses for Gram-negative bacteremia?

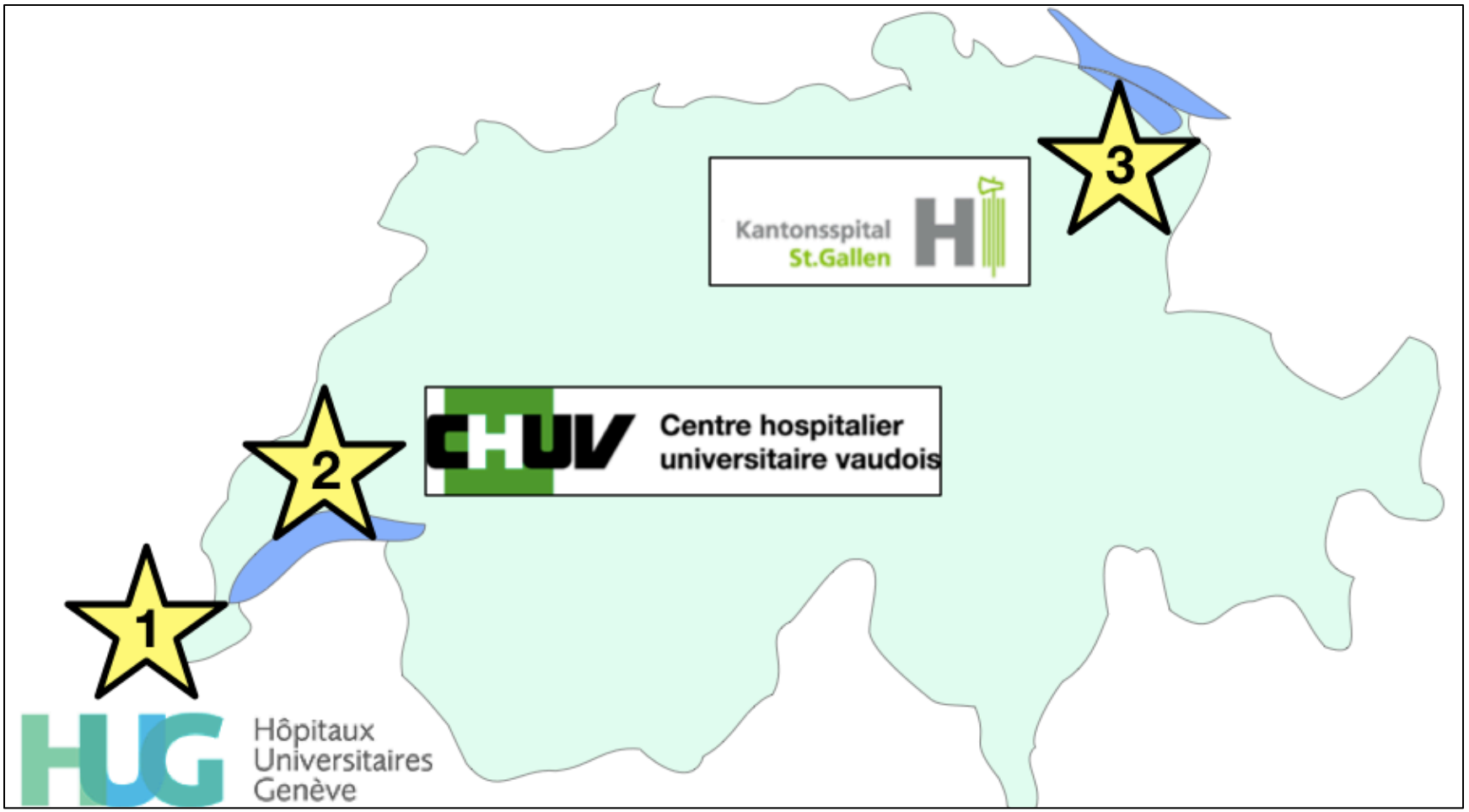
- **Gram-negative bacteremia is on the rise**
  - Patients are getting older, more co-morbid, and more immunosuppressed
- No RCT evaluating the optimal duration of therapy for Gram-negative bacteremia (GNB) has been published
- Some physicians give 14 days of antibiotics, some 7…and some even only 5 (“pseudo-randomizations”)
- Indirect evidence that, in patients without structural complications who are improving, shorter durations are safe

Havey TC, Fowler RA, Daneman N. *Crit Care.* 2011;15(6):R267; Sandberg T, Skoog G, Hermansson AB, et al. *Lancet.* 2012;380(9840):484-490; Chastre J, Wolff M, Fagon JY, et al. *JAMA.* 2003;290(19):2588-2598

Rationale for the PIRATE project

- So why not structure these pseudo-randomizations at the point of care and follow our patients' clinical outcomes?

The PIRATE trial's sites…



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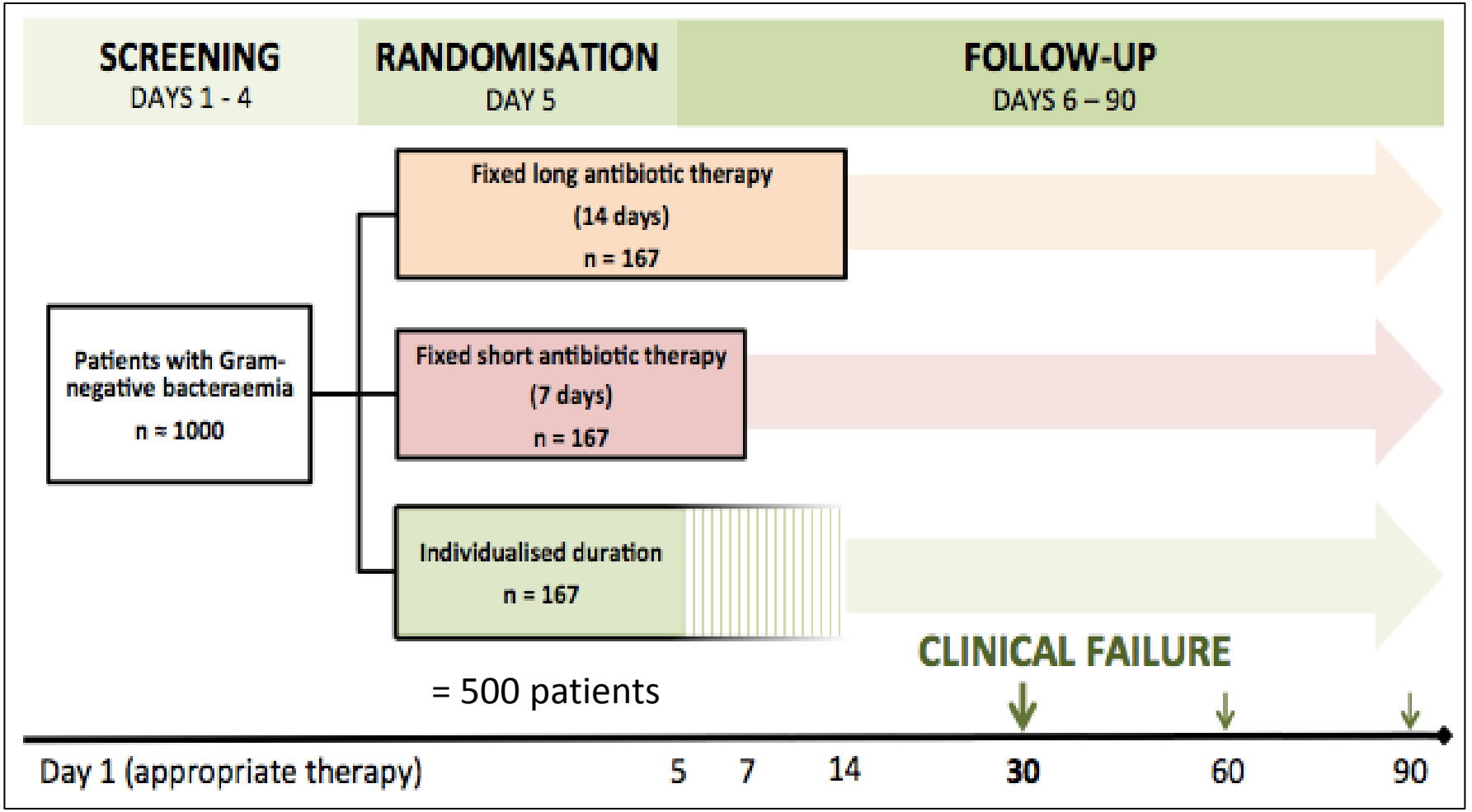
Study design

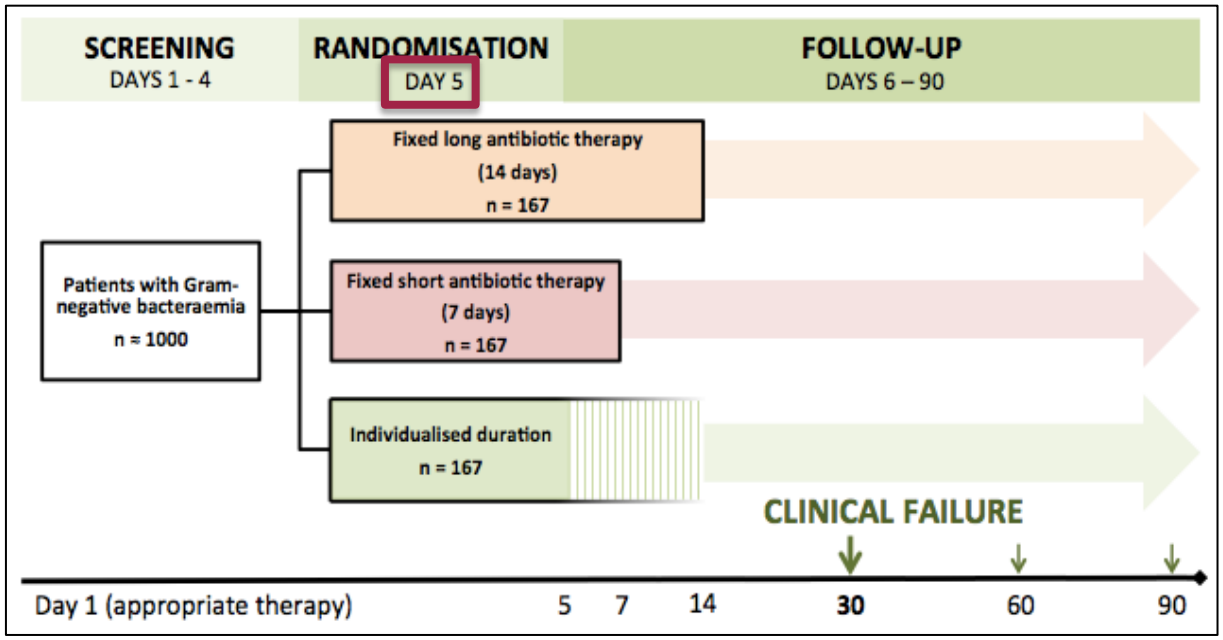
Randomized (1:1:1) controlled, triple-blind phase IV POC trial



Designated investigators & patients blinded until antibiotic discontinuation

Analyst blinded

Population, outcomes



Inclusion criteria:

1. Age ≥ 18 years
2. The presence of Gram-negative bacteria in at least one blood culture bottle
3. Treatment with a microbiologically efficacious antibiotic

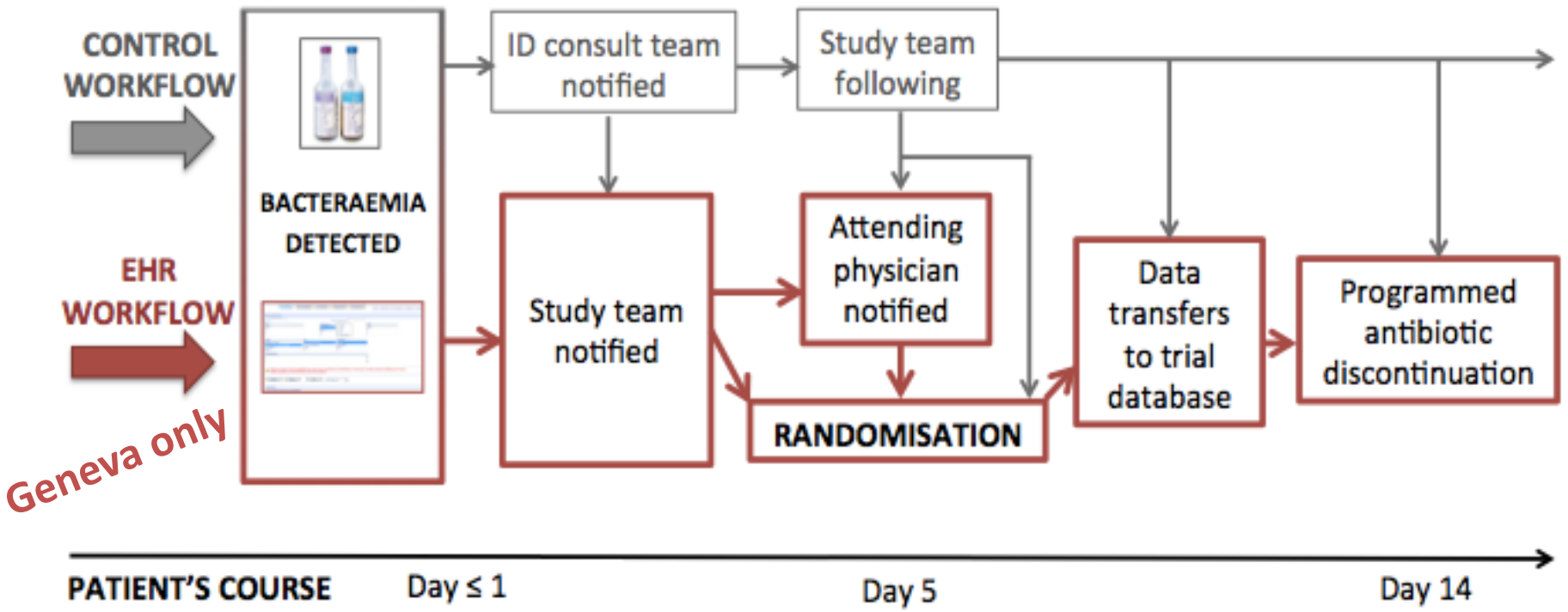
Exclusion criteria:

1. Immunosuppression
2. Abscess/ other complications
3. Certain "difficult" organisms
4. Etc….

Primary outcome = clinical failure = at least one of the following:

- **Relapse**: a recurrent bacteremia due to the same bacterium occurring from the day of treatment cessation through day 30
- **Local suppurative complication** not present at infection onset
- **Distant complications** of the initial infection, defined by growth of the same bacterium causing the initial bacteremia (as determined by antibiotic susceptibility profiling)
- **The restarting of Gram-negative-directed antibiotic therapy** due to clinical worsening suspected to be due to the initial infecting organism and for which there is no alternate diagnosis/pathogen suspected
- **Death** due to any cause through day 30

Study design: informatics component



Electronic-healthcare record workflow for patient identification, randomization and follow-up. The EHR workflow is outlined in red, the control ("back-up") workflow in grey. Grey arrows indicate safety valves; these cover all points at which the EHR workflow could malfunction. In this hypothetical case, the patient has been randomized to the control arm (antibiotic therapy duration of 14 days).

Study schedule (keeping it simple)

Study visit/observation point	1	2	3	4	5	6	7
	Screening	Randomization	Follow-up				
Timeline (days)	**0-4**	**5**	**8**	**12**	**30**	**60**	**90**
Window period (days)			±2	±2	±7	±14	±21
Informed consent	X	(X)			(X)	(X)	(X)
Entry criteria	X						
CRP measurement* (2ml blood)			(X)	(X)			
AEs reviewed					X		
SAEs reviewed					X	X	X
Other outcomes data collected					X	X	X

Study timeline

Geneva launch
1 April 2017

Lausanne &
St. Gallen launch
1 May 2017

Milestones	Preparation phase		Study period									Study close-out
	Year 1				Year 2				Year 3			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
	Jan - Mar 2017	Apr - Jun	Jul - Sept	Oct - Dec	Jan - Mar 2018	Apr - Jun	Jul - Sept	Oct - Dec	Jan - Mar 2019	Apr - Jun	Jul - Sept	Oct - Dec
Protocol development												
Contracts signed												
Ethics committee approvals												
Study dissemination, outreach												
Data management (EHR, eCRF)			(support)									
Patient recruitment												
Site monitoring												
Interim analysis					X							
Database cleaning, exports												
Database lock & analyses												
Manuscript preparation												
Publication, dissemination												

Two-year recruitment period

Opt-out / general information

5 – The safety valves: extensive investigator documentation of the initial encounter and self-monitoring with post-consent follow-up and mandatory reporting to the ethics committee

The obvious concern with the general information model is that it could represent a "slippery slope." If patients are not required to sign an informed consent form, investigators may be tempted to act paternalistically, assuming the patient's consent in most cases and subsequently cutting the corners so painstakingly established by the Geneva Conventions and later the Belmont Report and the Declaration of Helsinki.

For this reason we propose (1) a strict level of documentation by study investigators recording the initial encounter (time and place of occurrence, persons present, time required to present and explain the study and time needed by patient to decide on participation) and (2) self-monitoring of post-consent follow-up with required, regular reporting of results to the ethics committee. The monitoring will proceed as follows:

- All initially consenting patients will be re-contacted
  - Within two weeks following enrollment (± 5 days)
  - At days 30, 60 and 90
- And will be asked
  - Whether they remember consenting to participate in the trial
  - Whether they have specific questions pertaining to the trial

The results will be documented and sent to the principal investigator for compiling. They will then be sent bi-annually (four times over the two-year recruiting period) to the ethics committee. They will also be monitored regularly by the study's external monitor. Finally, the results will be compared to those of historical controls such as those published by Chenaud et al.[2] and published for the benefit of the clinical and bioethics communities (see secondary outcomes).

Ethics Commission's response…

Remarques générales		
Nous vous félicitons pour ce projet qui sort du lot autant pour le fond que pour la forme	We thank the Commission for this kind assessment.	
Ecrans 1-3 **(correspond à l'ancien formulaire de base)**		
1. A l'écran 2, est-il justifié de dire que votre étude est « double-blind » ?	We agree; we have removed this description from the form.	
Formulaire d'information		
2. Nous encourageons les efforts qui visent à améliorer le processus de consentement, mais en l'état, le degré de simplification n'est pas évident car il s'agit en fait simplement de donner un formulaire d'information ordinaire puis de documenter leur consentement dans une note de suite plutôt que de leur demander de signer le document usuel. En soi ce n'est pas une mauvaise idée, mais il y a deux hics : • La loi suisse requiert la forme écrite pour le consentement à la recherche. Ce point est abordé dans le commentaire ci-dessous, et la solution de faire signer un témoin est effectivement réalisable. Elle aurait l'avantage de faire intervenir une tierce personne susceptible d'aider le participant potentiel à prendre sa décision, mais l'inconvénient qu'il faudrait à chaque fois trouver une telle personne, qui ne peut être affiliée à l'étude.	• We understand and have amended the protocol and informed consent to allow for a witness unrelated to the study to sign the consent form once the patient has been fully informed and has consented.	Protocol v1.1 p.33, Section 8.3, and p.28, Section 6.1

Ethics Commission's response…

• On distingue le formulaire d'information du formulaire de consentement. Or, ce dernier a un contenu, qui est perdu ici. Il faudrait le cas échéant importer ce contenu dans le formulaire d'information.	• We have now added the consent form to the information brochure.	
Auriez-vous la possibilité de comparer les diverses formes de consentement (taux d'acceptation, compréhension etc.) à l'intérieur de votre protocole et de nous soumettre une proposition ? Des questionnaires standardisés existent déjà (contacter samia.hurst@unige.ch pour plus de renseignements si nécessaire)	• We have now included in the study protocol the proposal, previously described in Appendix 1, to compare the different forms of consent. This is now described, with more methodologic detail, as a nested, prospective observational cohort study.	Protocol v1.1 p. p.28, Section 6.1
3. Document « streamlined ic » justifiant l'obtention du consentement oral des participants : Selon l'OClin, les seules exceptions à la forme écrite du consentement sont les suivantes: a. lorsque, pour des raisons corporelles ou cognitives, la personne concernée ne peut pas lire ou écrire; et b. lorsque l'investigateur apporte la preuve de l'information et du consentement, notamment par le biais d'une attestation écrite de témoins ou de l'enregistrement du consentement donné verbalement. Nous vous recommandons d'opter soit pour l'attestation écrite du témoin soit pour l'enregistrement du consentement donné par le patient à l'oral (OClin art.8 al.1b).	We have amended the protocol and informed consent to allow for a witness unrelated to the study to sign the consent form once the patient has been fully informed and has consented.	Protocol v1.1 p.33, Section 8.3, and p.28, Section 6.1

Written vs. oral consent: a substudy!

Informed Consent (follow-up)

1. **Does the patient remember that he/she is participating in this study ?**
   ○ yes ○ no
2. **Does the patient remember that he/she granted consent to participate ?**
   ○ yes ○ no
3. **Does the patient remember the purpose of the study ?**
   ○ yes ○ no
4. **Does the patient remember the risks of the study (as described at enrollment) ?**
   ○ yes ○ no
5. **Does the patient have questions now related to the study ?**
   ○ yes ○ no

ved by

Reason
Project version --

About that external validity…

- How representative are our included patients?

- EPCO: Excluded patients' outcomes
  - Prospective observational study examining PIRATE's primary outcome in those we didn't enroll

The study that still needs to be done

- Metagenomic analysis of the microbiota in patients who had shorter versus longer antibiotic courses:

Will we indeed decrease the number of antibiotic resistance genes (ARG) that we carry (and transmit)?

Comments, questions?

Thank you