Ethical issues with studies in Healthy Volunteers in resource-poor settings

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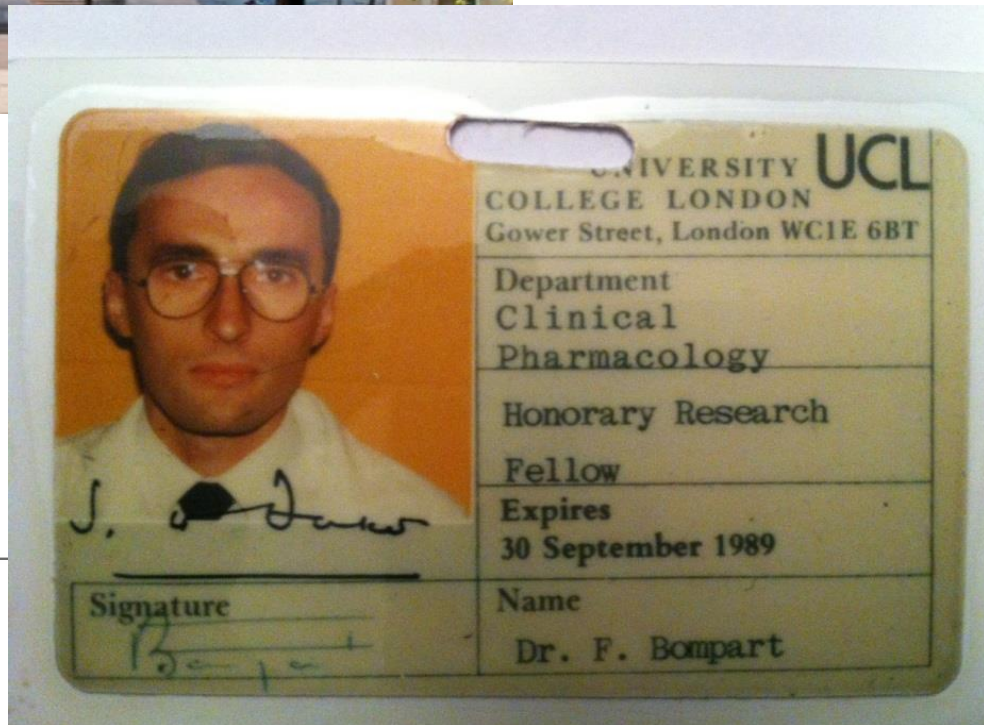
Background:
healthy volunteers in the 1980s



Healthy volunteers
Everywhere in the world

- Are exposed to risks of harm for the potential benefit of others: patients and society

- Only benefit financially from their participation in a study

- Deserve “specifically considered protection”

  “Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm… All vulnerable groups and individuals should receive specifically considered protection”

  World Medical Association´s Declaration of Helsinki (2013 §19)

Healthy volunteers
In resource-poor settings

- Often poor people with low literacy levels
  - May not understand the risks they may take
- Participation in clinical trials is critical source of income.
  - Not in a position to refuse financial incentives
- “Professional healthy volunteers” develop tactics to conceal involvement in several studies and to hide medically relevant information
  - Experts in inclusion/exclusion criteria

Potential risks

- **Safety risks for volunteers**
  - Drug-drug interactions, cumulative toxicity if no respect of wash-out periods between studies
  - Side effects if medically significant information is hidden

- **Reputational risks for the Pharmaceutical Industry**
  - Healthy volunteers: vulnerable group
  - Pharmaceutical firms sponsor most studies in healthy volunteers
  - Risks related with working with third parties (CROs)

- **Data validity risks**
  - Risk of unsound scientific data if no respect of wash-out periods between studies and medical information is hidden

Sanofi Bioethics Committee's working group on healthy volunteers

Available data

Healthy volunteers in resource-poor settings. A poorly-documented field

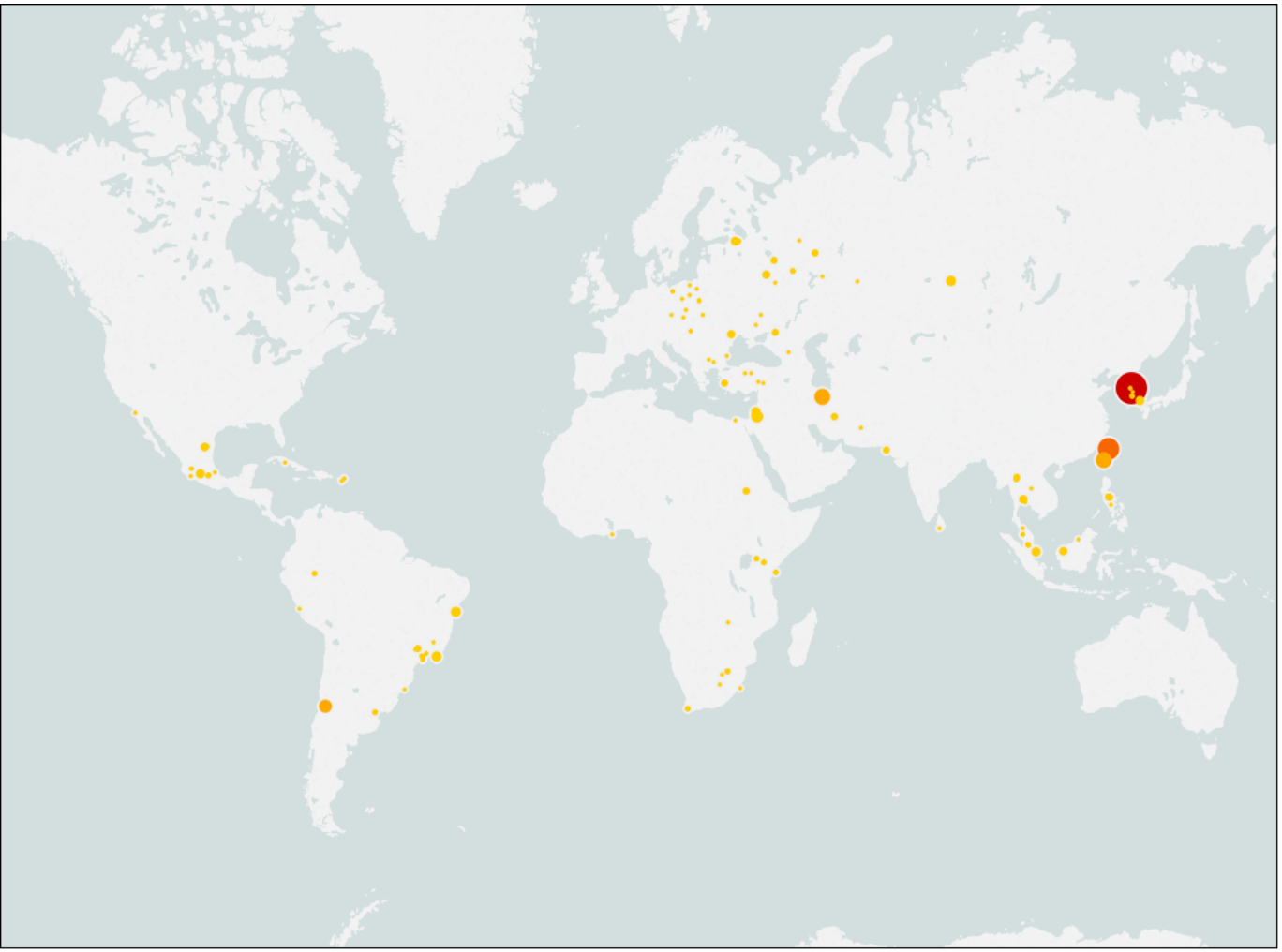
No data-based publication found on global use of heathy volunteers in clinical research

Phase I trials publication on public databases not compulsory

Commercial interests limit access to data (Pharmaceutical firms and CROs)

Databases search:
« Phase I trials with sites in emerging countries »

Phase I trials distribution map (SiteTrove dashboard)



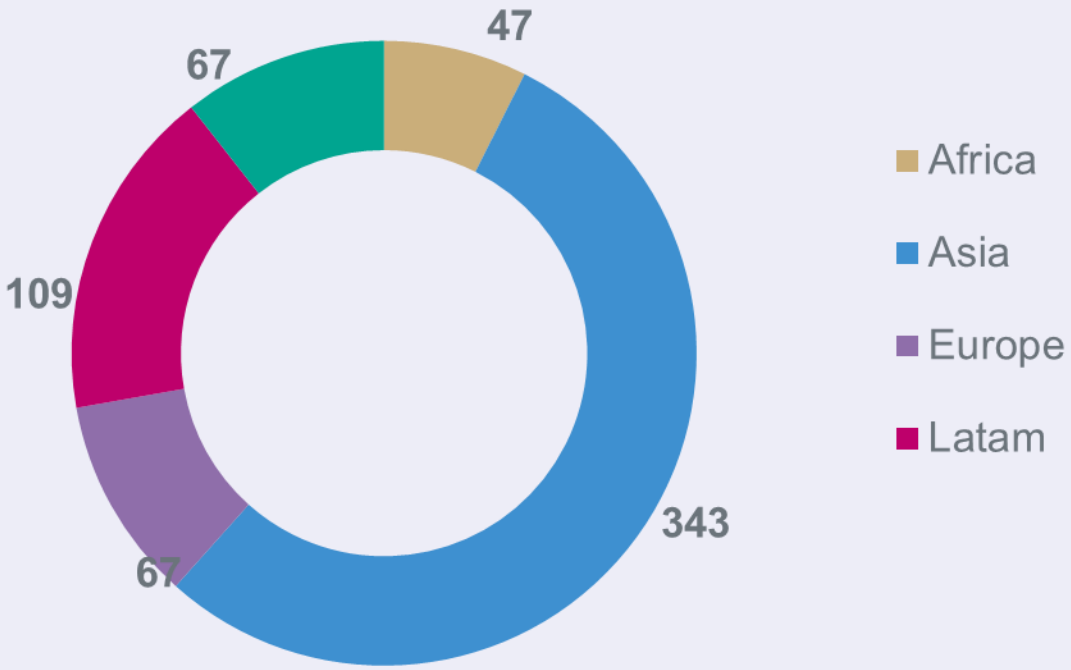
Investigators by State/Province/County

Country	
Argentina	3
Bangladesh	2
Brazil	44
Bulgaria	3
Burkina Faso	2
Chile	10
Cuba	18
Czech Republic	2
Egypt	1
Gabon	3
Georgia	1
Ghana	1
Hungary	2
Islamic Republic of Iran	22
Israel	33
Jordan	3
Kenya	6
Lebanon	2
Malawi	2
Malaysia	13
Mali	7
Mexico	23
Nepal	1
Pakistan	3
Panama	1
Peru	7
Philippines	10
Poland	11
Puerto Rico	3
Republic of Korea	169
Republic of Moldova	4
Russian Federation	41
Singapore	60
South Africa	9
Sri Lanka	1
Sudan	3
Taiwan	65
Thailand	19
Tunisia	1
Turkey	7
Uganda	4
Ukraine	4
United Republic of Tanzania	7

Databases search:
« Phase I trials with sites in emerging countries »

Distribution of Investigators

- **Phase I trials Investigators per region**



Source: SiteTrove, June 9th 2017

Scientific litterature review

- Several publications on financial motivations as key determinant for healthy volunteers' participation
- Some US publications address the issue of « professional healthy volunteers » and « research underclass »
- Publications from: india (1), Romania (1), Israel (1), Brazil (1)
- Informed consent process rarely addressed:

  In a 2005 Israeli study: out of 100 participants, only **35% reached a « quality decision ».**

  58% of the volunteers do not **seek out information nor check alternatives before making a decision.** C. Rabin et al Issues in Clinical Nursing doi: 10.1111/j.1365-2702.2006.01388.x

Sanofi-sponsored studies in healthy volunteers

Sanofi-sponsored studies in Healthy Volunteers: Years 2014, 2015 and 2016

Studies performed	Type of studies	Healthy volunteers involved	Studies per country
122	Pharmacokinetic studies : 113 « Fist-in-man » single or multiple ascending doses studies: 9	Approximately 4800* *Average number for bioequivalence studies: 40 volunteers	**Canada = 40** **Brazil = 19** **Romania = 15** **Czech Rep = 8** **Germany = 7** **US/Canada = 6** **France = 5** **US = 4** **India = 4** **Malaysia = 4** **China = 3** **Indonesia = 2** **Turkey = 2** **Korea = 1** **Japan = 1** **South Africa= 1** **Bulgaria = 1**

Rationale for selection of countries / study sites

- Regulatory requirements
- Preferred CROs : cost / quality / speed
- Ease of administrative processes
- Logistical issues (supplies shipment, packaging requirements, etc.)

What could be done to address vulnerability of healthy volunteers ?

Two cornerstones for ethical and safe participation of healthy volunteers

1. Informed consent process: ability to freely accept or refuse participation

- Ability to assess risks related with participation = literacy level
- Ability to refuse financial incentives which could override perceived risks = income level

2. Minimization of exposure to risk

- Respect of wash-out periods between studies
- No concealed underlying medical conditions
- Respect of instructions on concomitant medications, drugs, alcohol, diet, etc.

Potential solutions

- **Informed consent of people with low literacy levels**
  - Perform tests to assess ability to truly understand information
  - Recruit only people with pre-defined literacy level
- **“Professional healthy volunteers” concealing involvement in multiple studies**
  - National registries of healthy volunteers
- **Clinical trials as critical source of income**
  - Cap maximum yearly payments through national registry of healthy volunteers

National registries of healthy volunteers

- France since 1988
  - Yearly cap on payments to the same person: 4,500 Euros/year
- Brazil, Morocco, Jordan: under development (?)
- Some US academics advocate for national registry (Devine et al 2013, Resnik / McCann 2015)

Proposal to the TRUST initiative

Healthy volunteers issue within the TRUST initiative

- Sub-group on ethics of volunteers in resource-poor settings
  - Doris Schroeder, UK, TRUST initiative leader
  - Vasantha Muthuswamy, Forum for Ethics Review Committees in India
  - Klaus Leisinger, Foundation Global Values Alliance (formerly Novartis)
  - Dafna Feinholz, UNESCO
  - François Bompart, Sanofi and EFPIA

Healthy volunteers issue within the TRUST initiative: what could we do ?

1. Collect information

- **Internal data from Pharma companies**
  - Countries where studies are performed
  - Rationale for countries selection
  - Processes for study sites and CROs selection, etc.
- **Look for case-reports in « TRUST » countries**
- **Collect best national practices : registries, local legislation and other safeguards for healthy volunteers protection in key countries**

2. Address the issue, e.g.

- Propose tests to check understanding of informed consent
- Advocate for establishment of national registries

Vision

2004: GSK announced the first online publicly accessible Clinical Study Register by a pharma company

2018: TRUST Pharma partners announce that they

- Will implement tests to check healthy volunteers' understanding of basic informed consent information

- Intend to stop performing clinical trials in countries with no healthy volunteers registry by 2023.