Simulated Clinical Trials

Principe - State of art - Covariate distribution models

Workshop "Modélisation et simulation d'essais cliniques"

Thuesday 09 April 2015

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Make use of the **available knowledge** about

- drug
- patients
- disease progression
- clinical program

to investigate **in silico** aspects of the clinical study plan

- dose regimen
- study design
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in order to make **rational, informed decision** with regards to **optimizing** the development plan of a new compound

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Controllable variables of a Clinical Trial may be referred to as **design properties**

- **Population properties** select subjects from the population
  - range of age, of weight, renal function, proportion males / females,...
  - inclusion and exclusion criteria in trial protocol
- **Treatment properties** specify the relationship patient / treatment
  - nature of treatment for each group (dose size, formulation, frequency,..)
  - kind of treatment assignment (design)
    parallel group, cross-over, forced titration, dose escalation,
    adaptive designs (**Talk of Raphael Porcher**), SMART design (DTR)
  - Method of treatment assignment : randomization
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To perform a SCT, **available knowledge** are needed. It may comes from

- previous Phase or previous studies (historical database)
- litterature and / or other databases

  Meta-Analysis $\Longrightarrow$ **Talk of Gilles Chatellier**
  Database merging $\Longrightarrow$ **Talk of Chloé Diméglio**
  Database sharing $\Longrightarrow$ **Talk of Anne-Cambon Thomsen**

together with 3 **technical machineries**

- **Covariate Distribution Model :** How to generate virtual patients ?
- **Input / output Model :** How covariates impact the outcomes ?

  PK / PD Models $\Longrightarrow$ **Talk of Jérémie Guedj**
  Disease progression models (predictive models)

- **Execution Model** : What can happens during the CT ?

  recruitment dynamic $\Longrightarrow$ **Talk of Vladimir Anisimov**
  missing data $\Longrightarrow$ **Talk of Grégory Guernec**
  patients drop-out
  compliance to treatment

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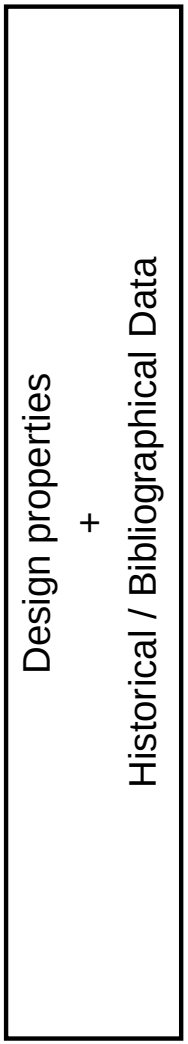
Example of SCT's scheme



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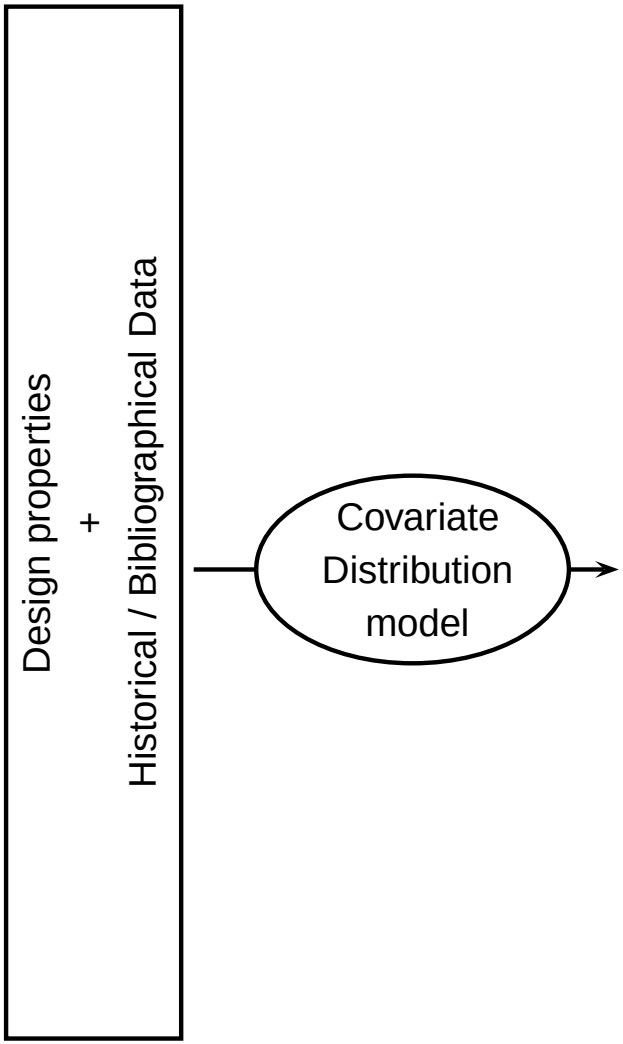

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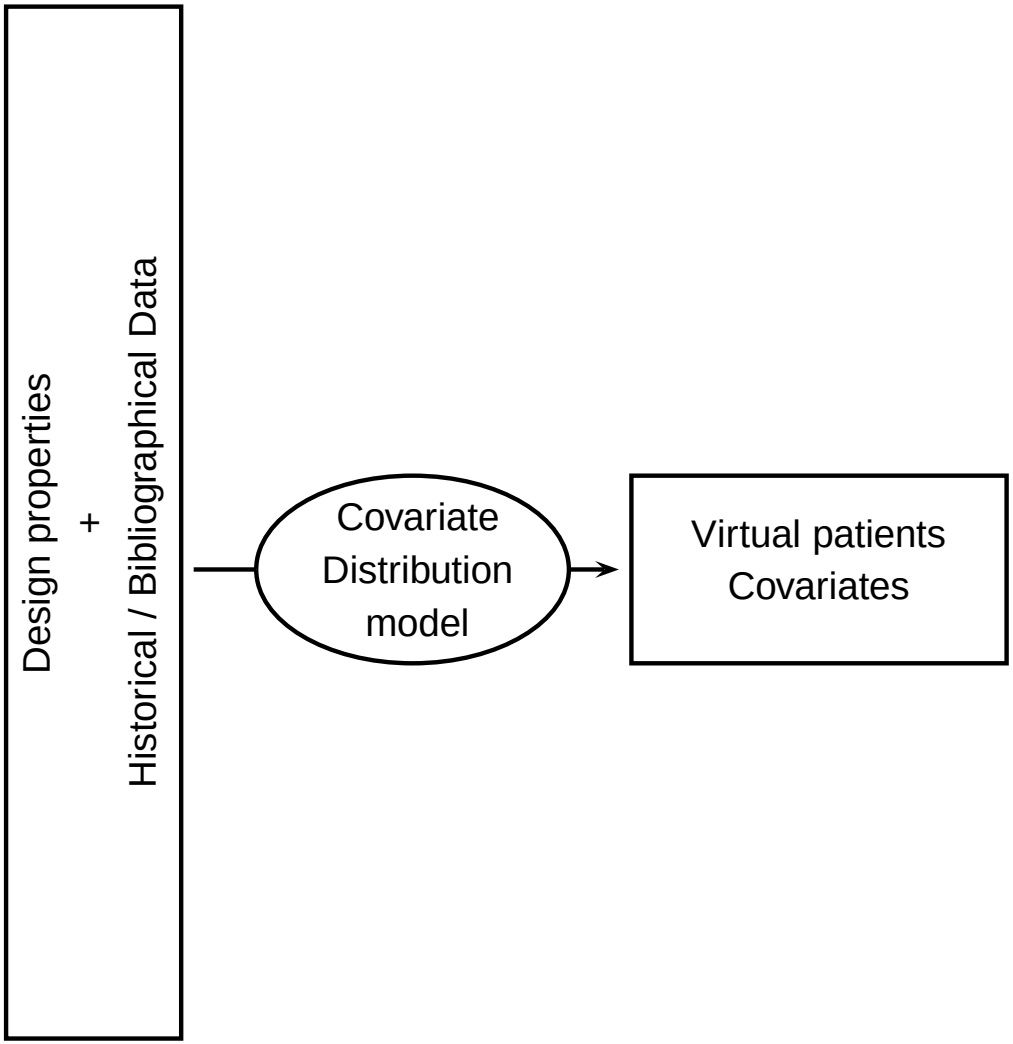

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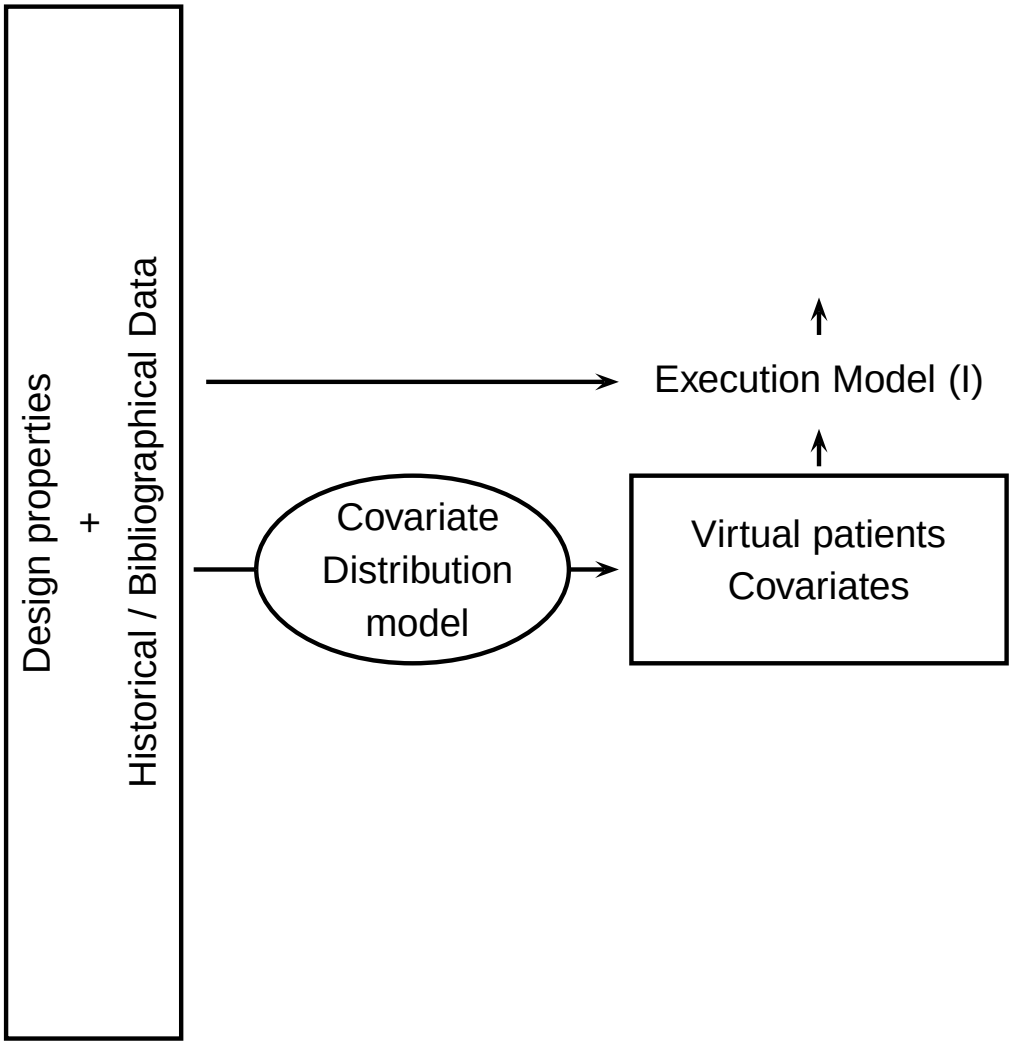

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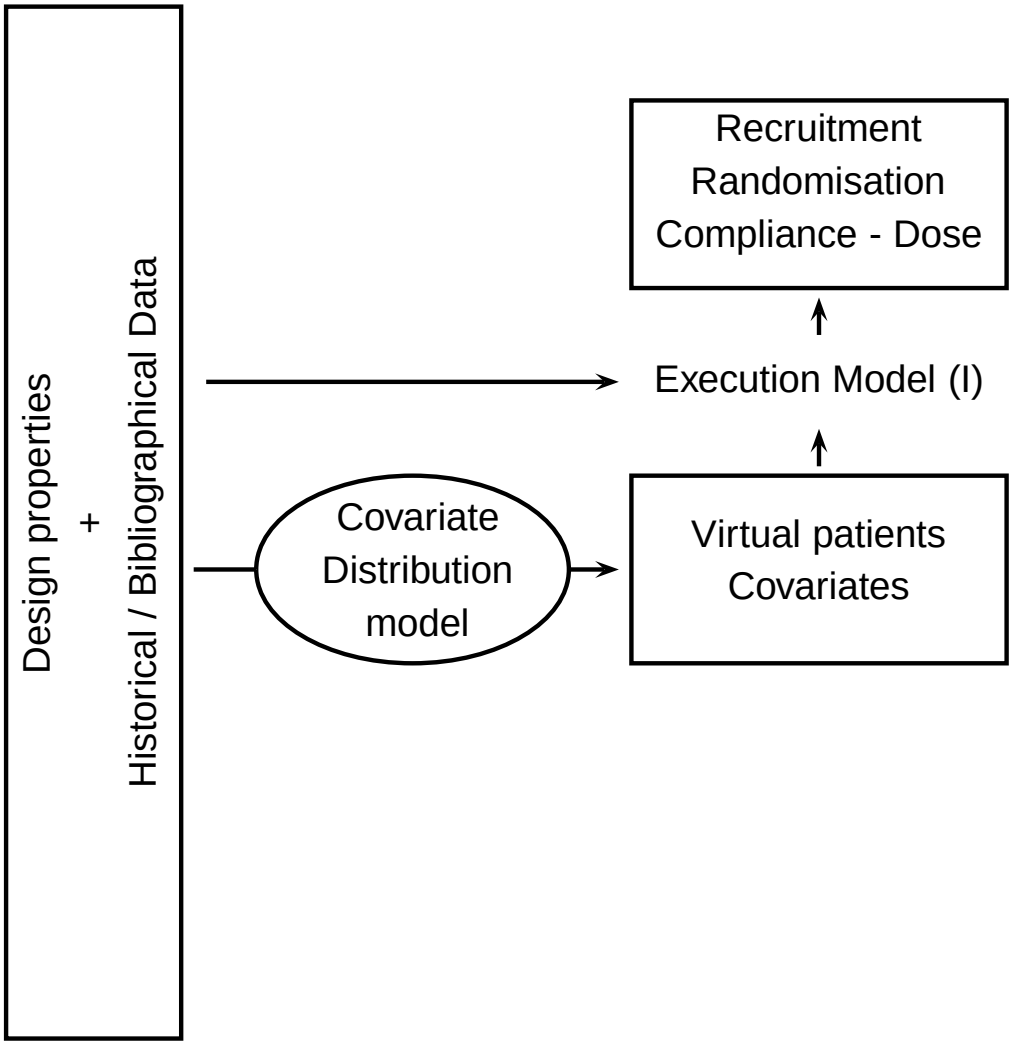

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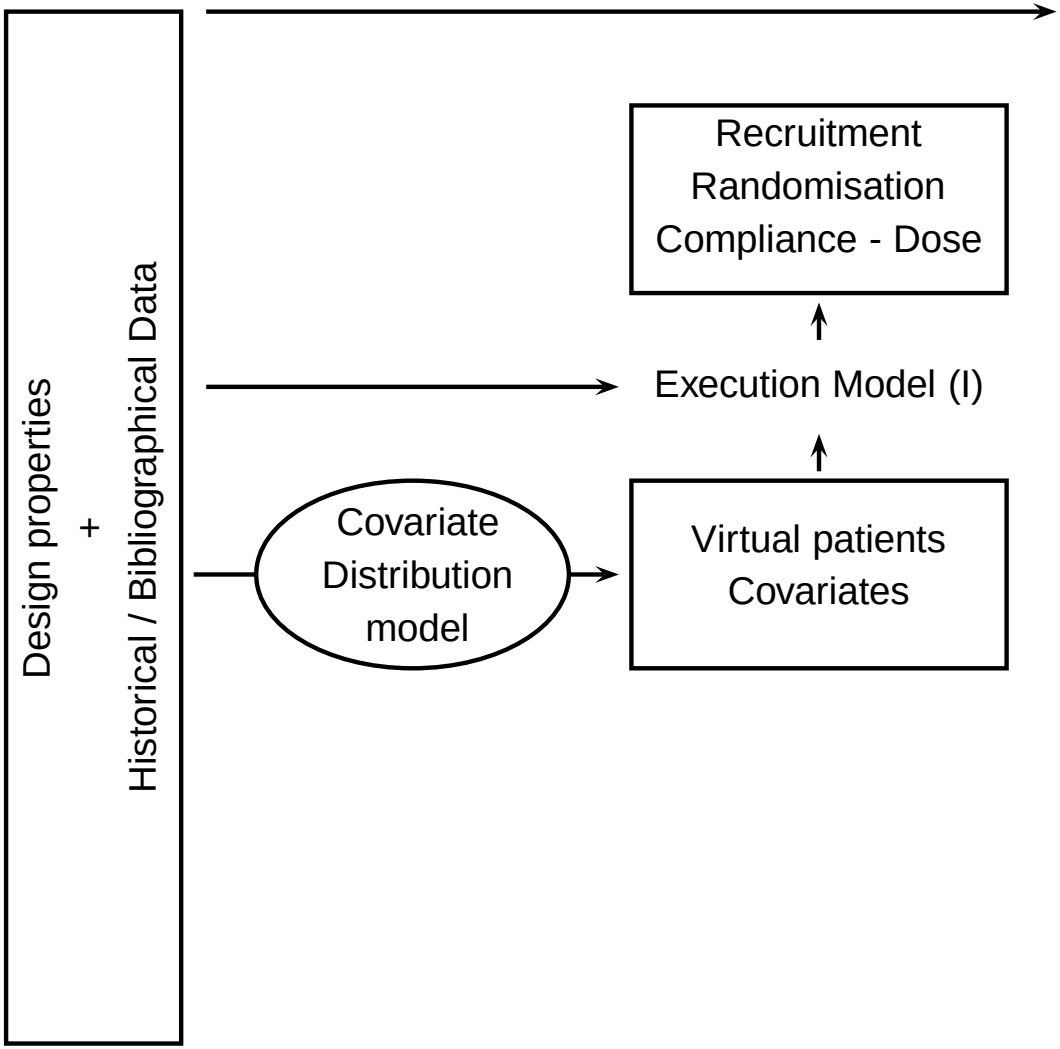

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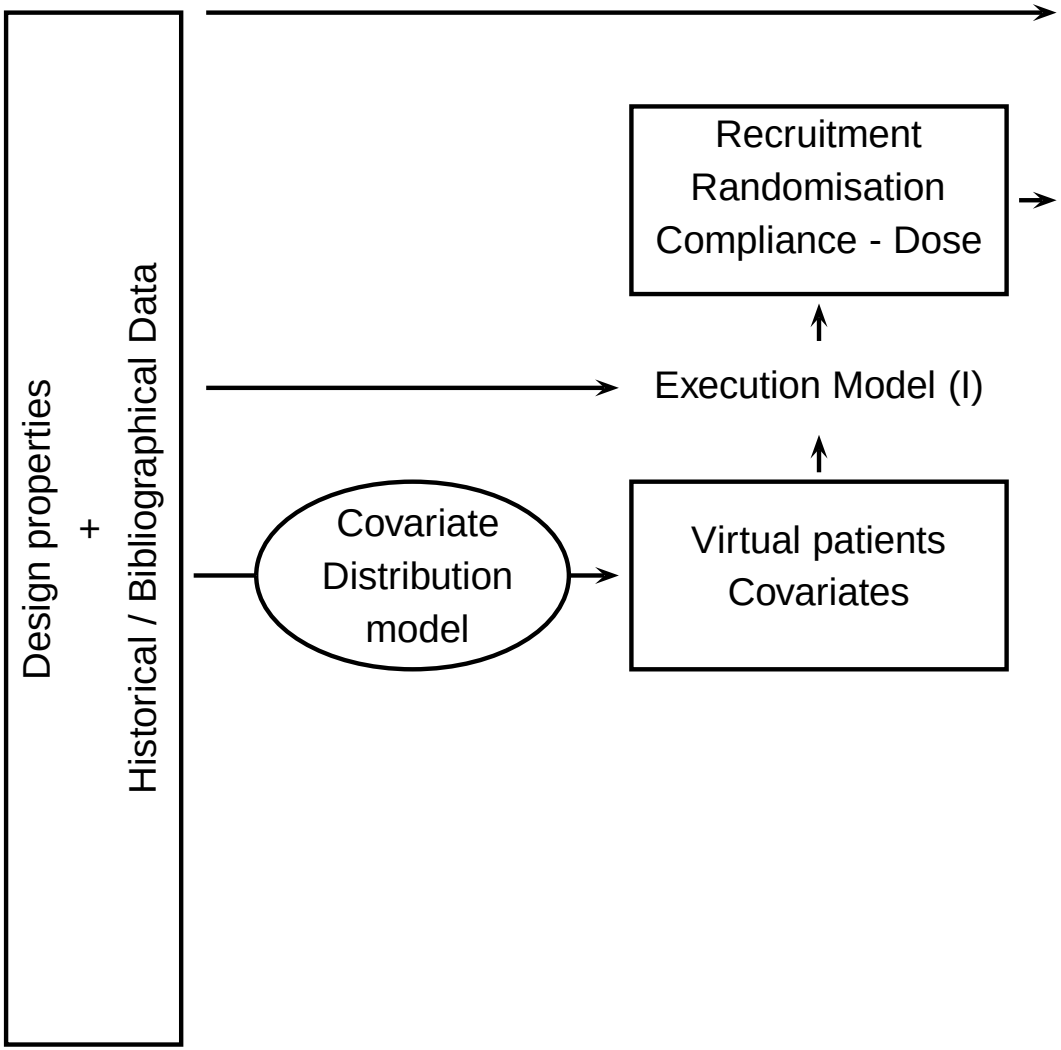

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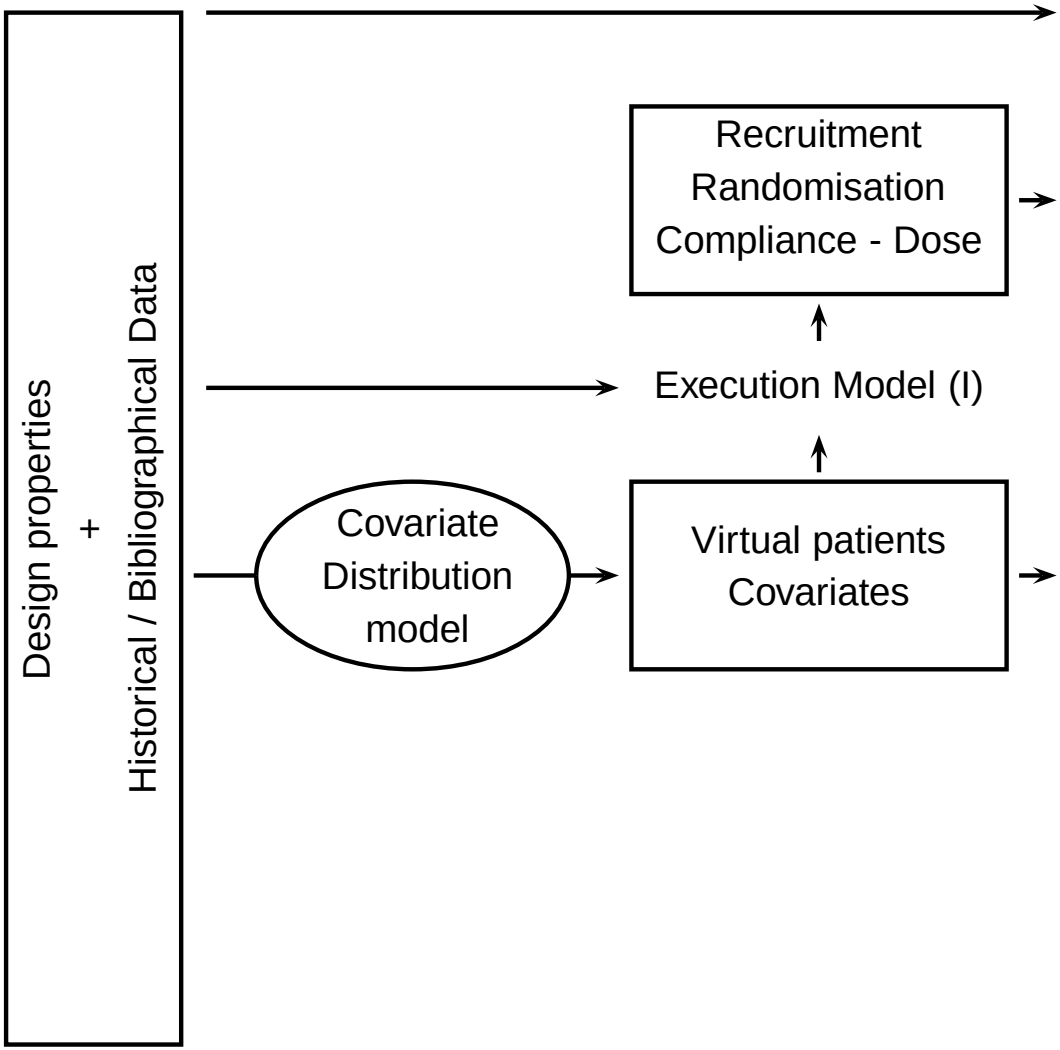

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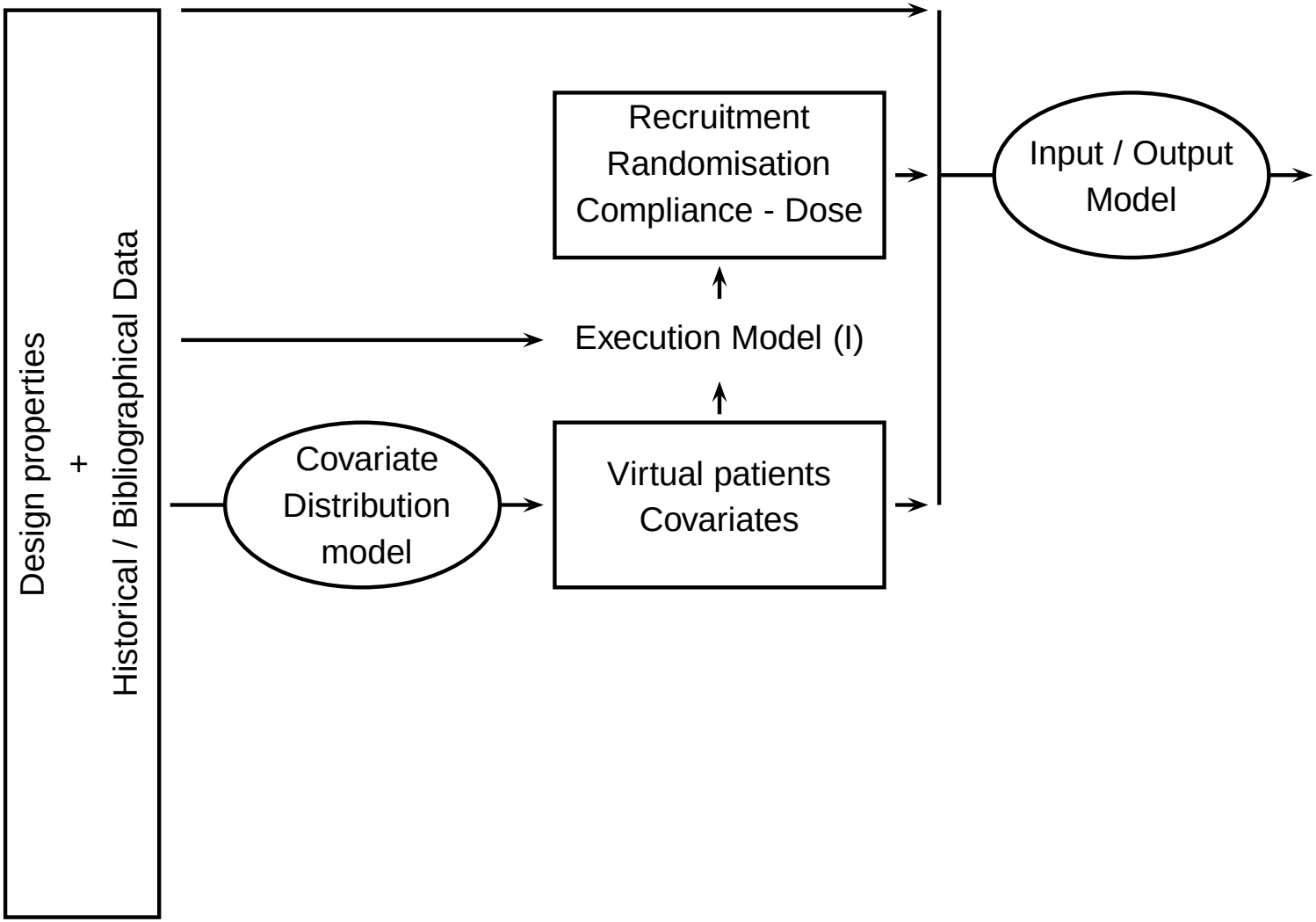

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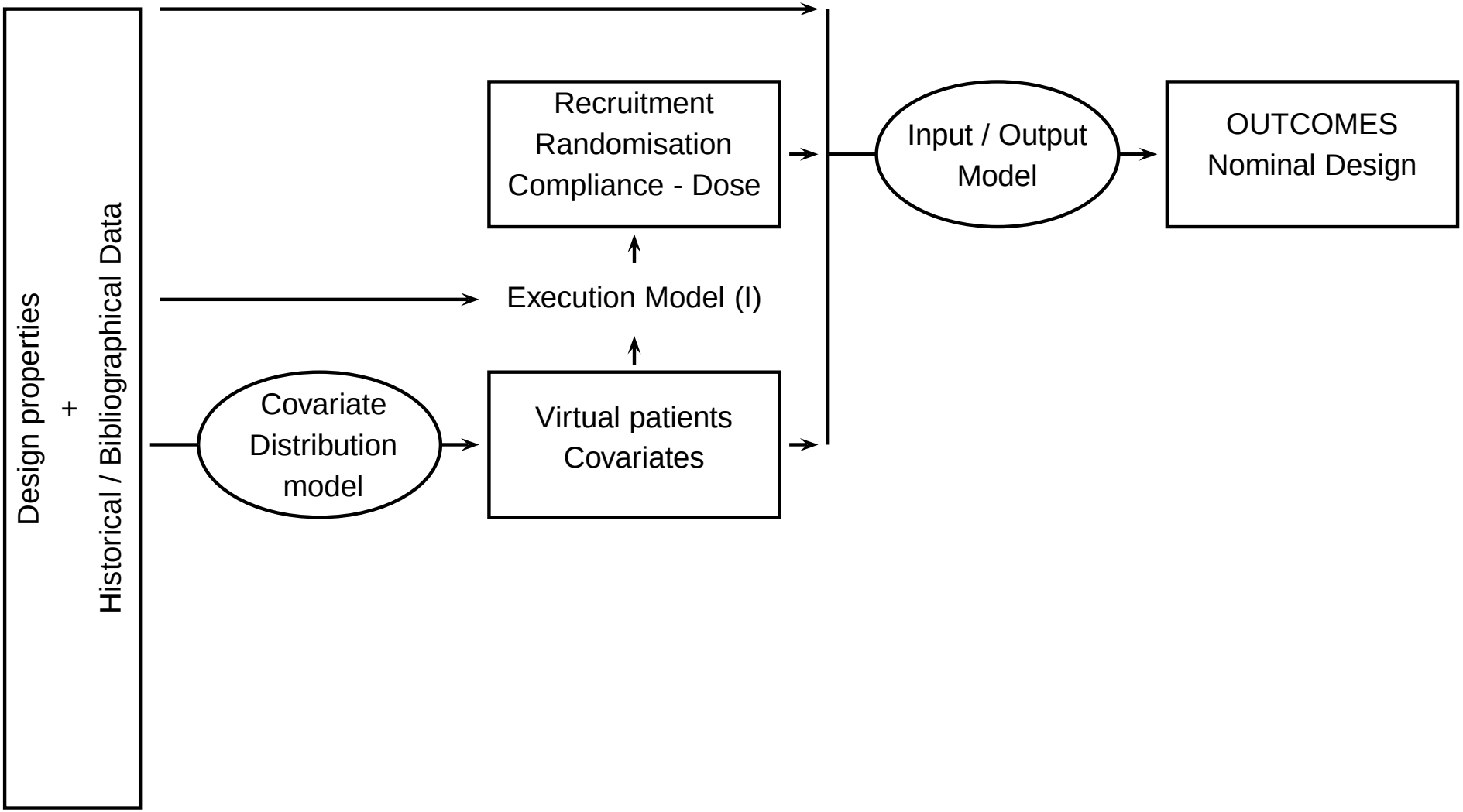

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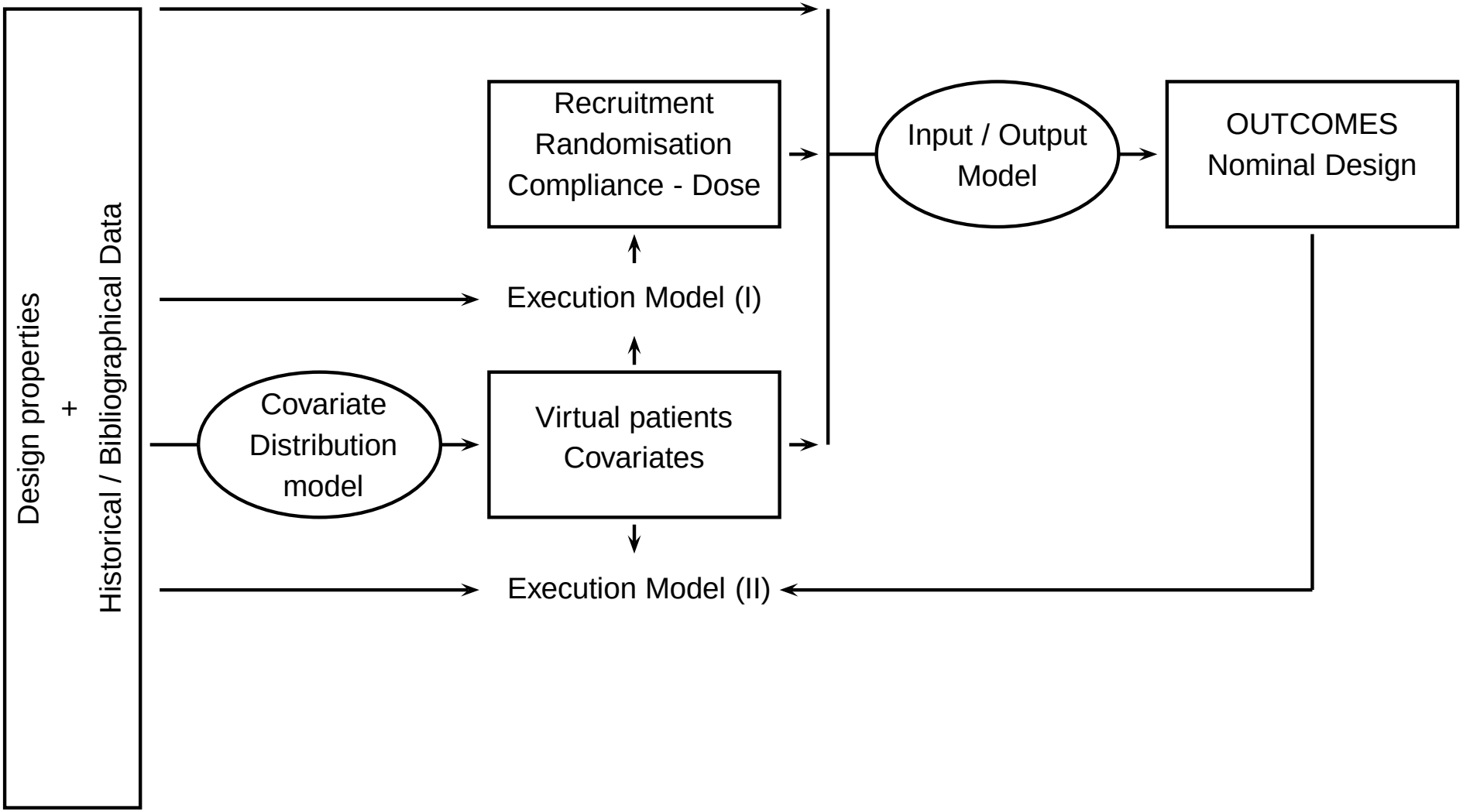

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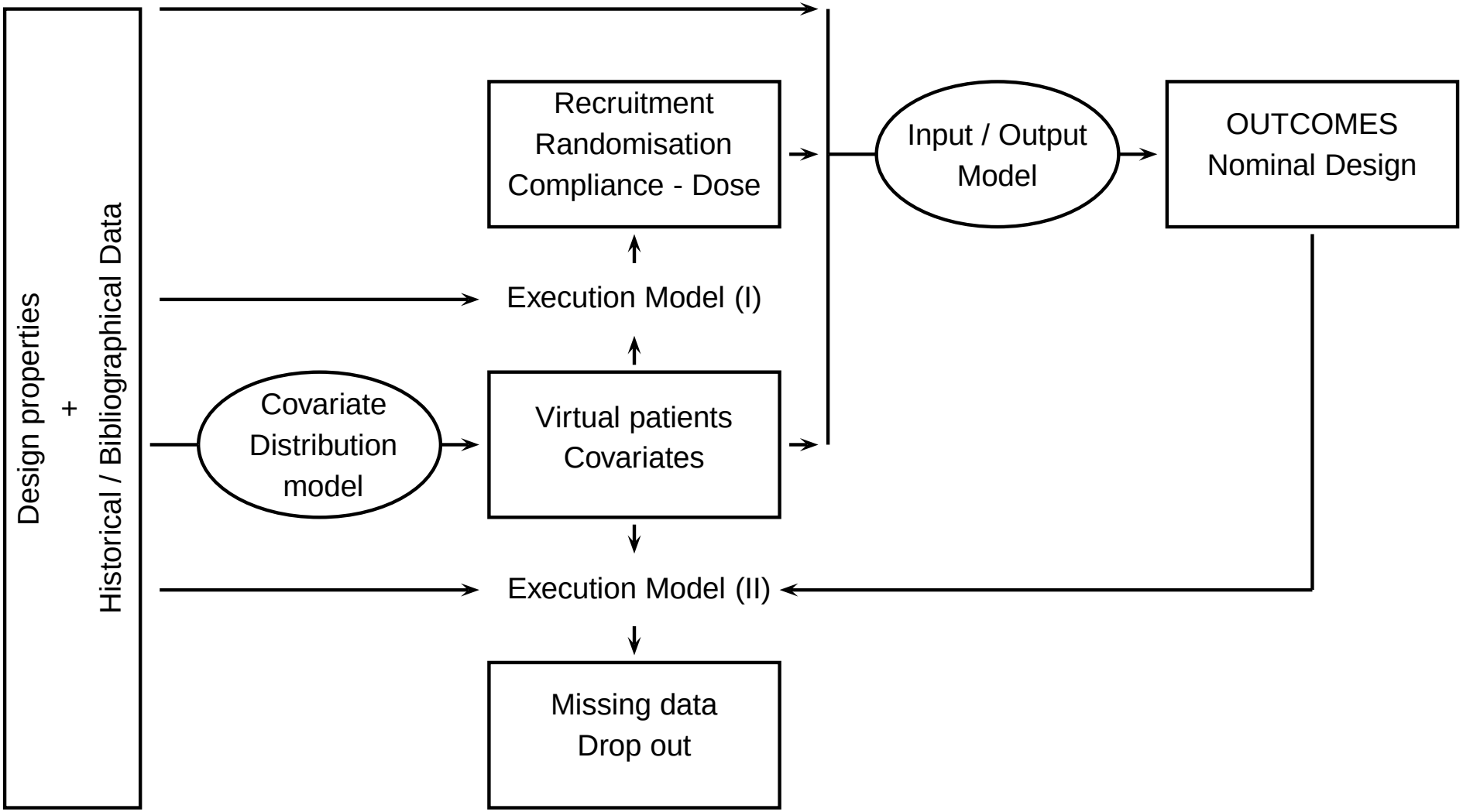

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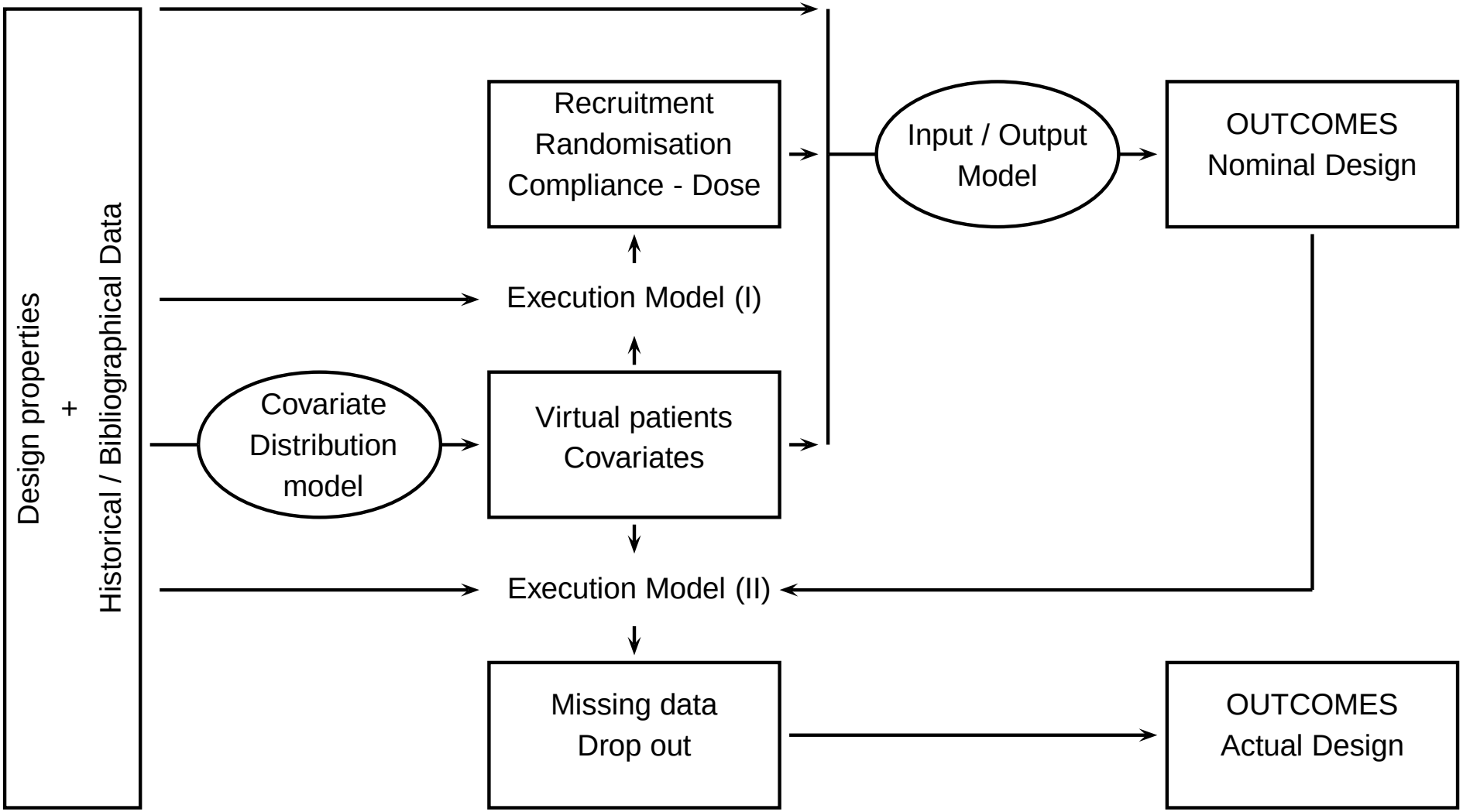

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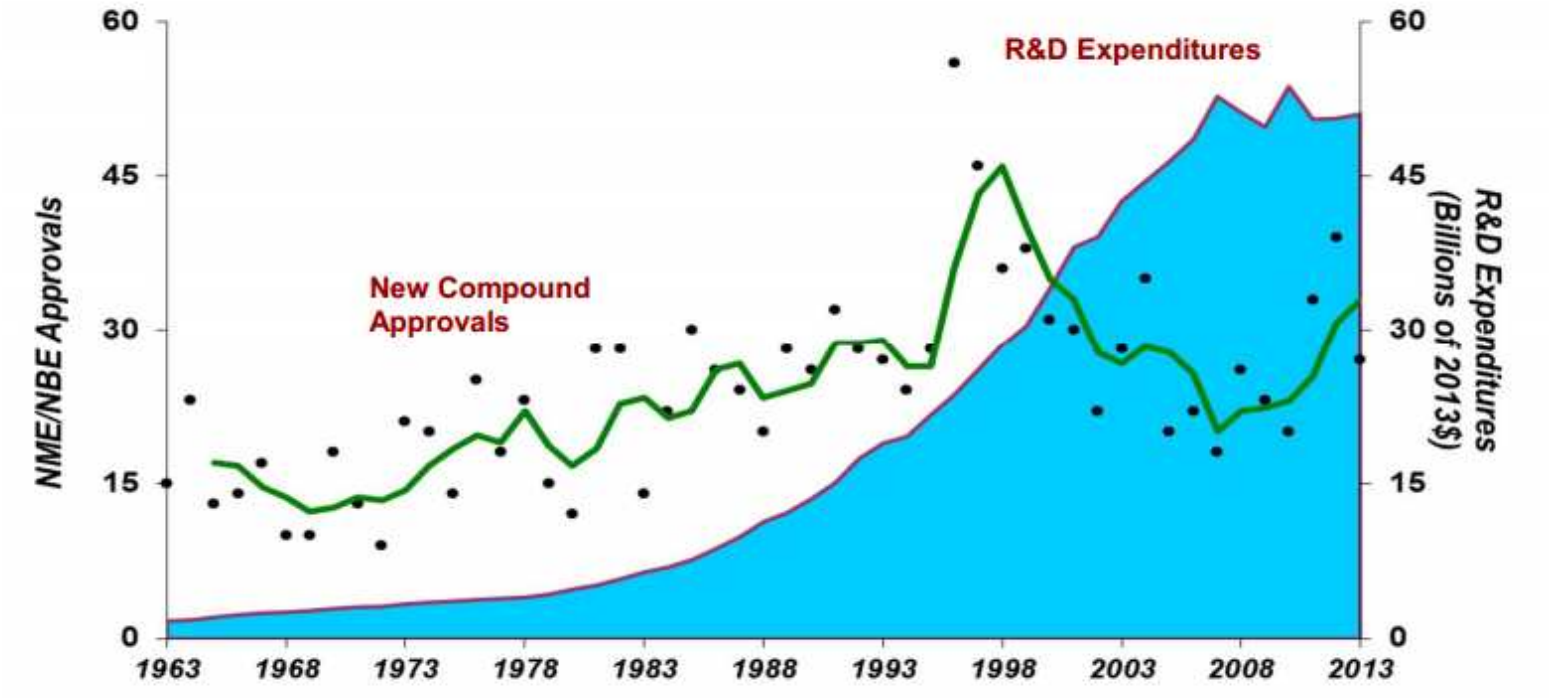

FIGURE: Source : Tufts CSDD ; PhRMA, 2014 Industry Profile

- Necessity to develop **efficient** design / measurement tools $\Longrightarrow$ complex designs
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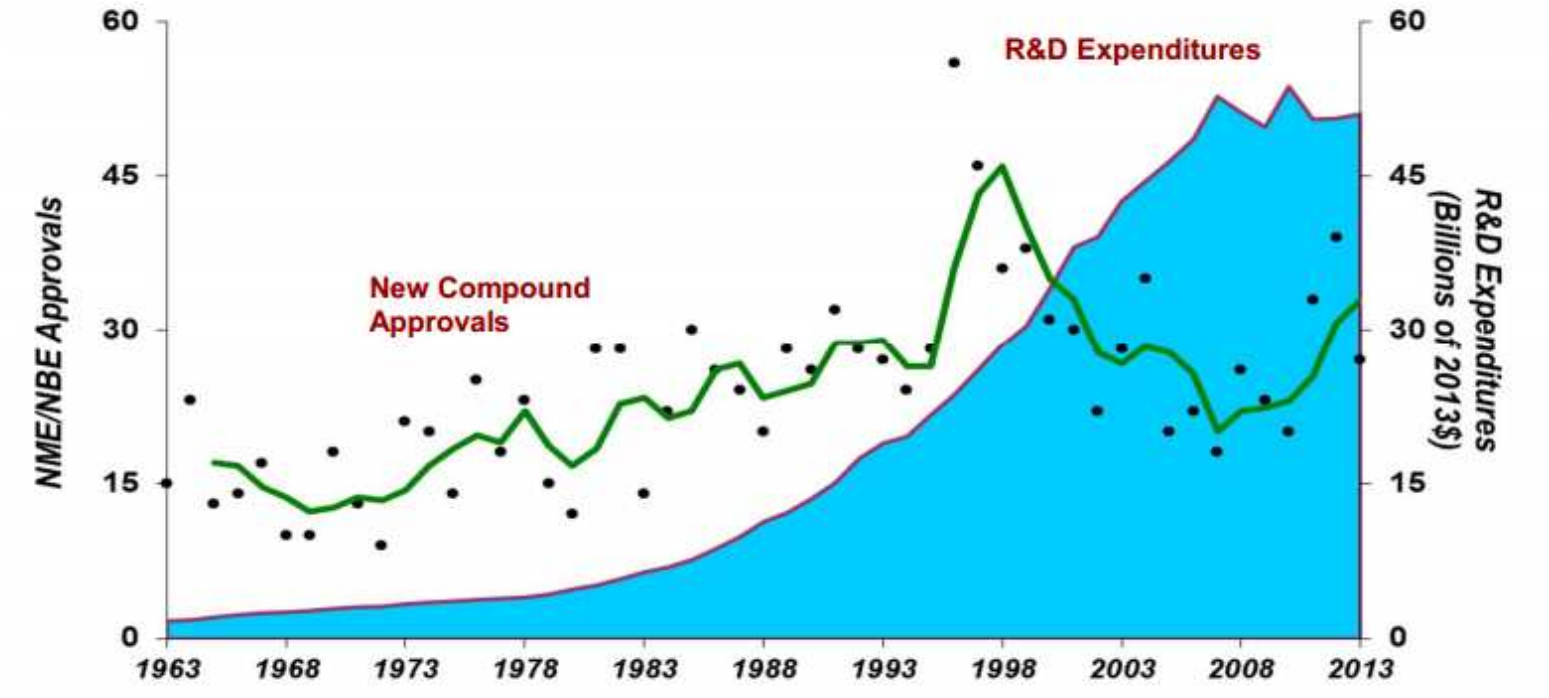

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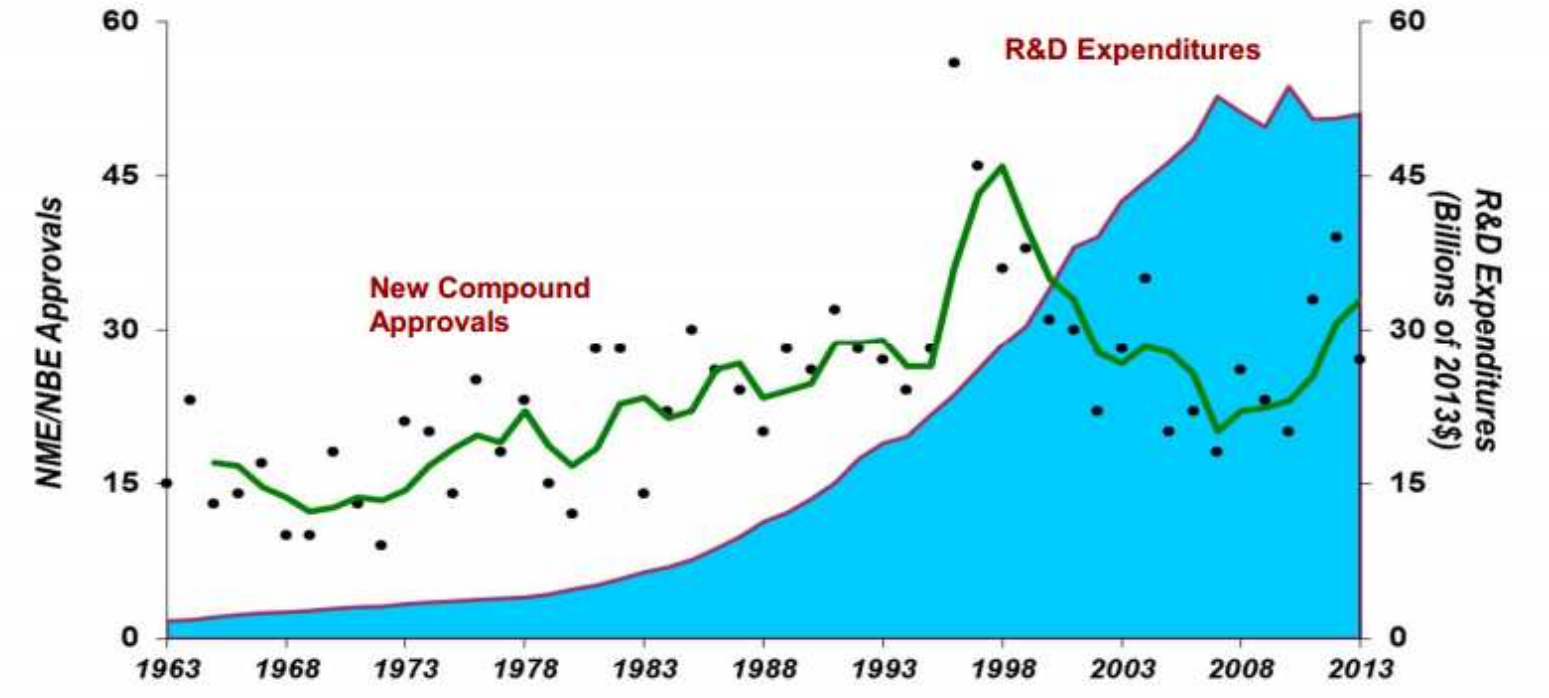

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- The **data sharing** pulse makes databases easily available

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- **No guideline** on how to do M-S
- Guideline on reporting results of population PK analyses (CHMP/EWP/185990/06) describes **expectations of EMA**
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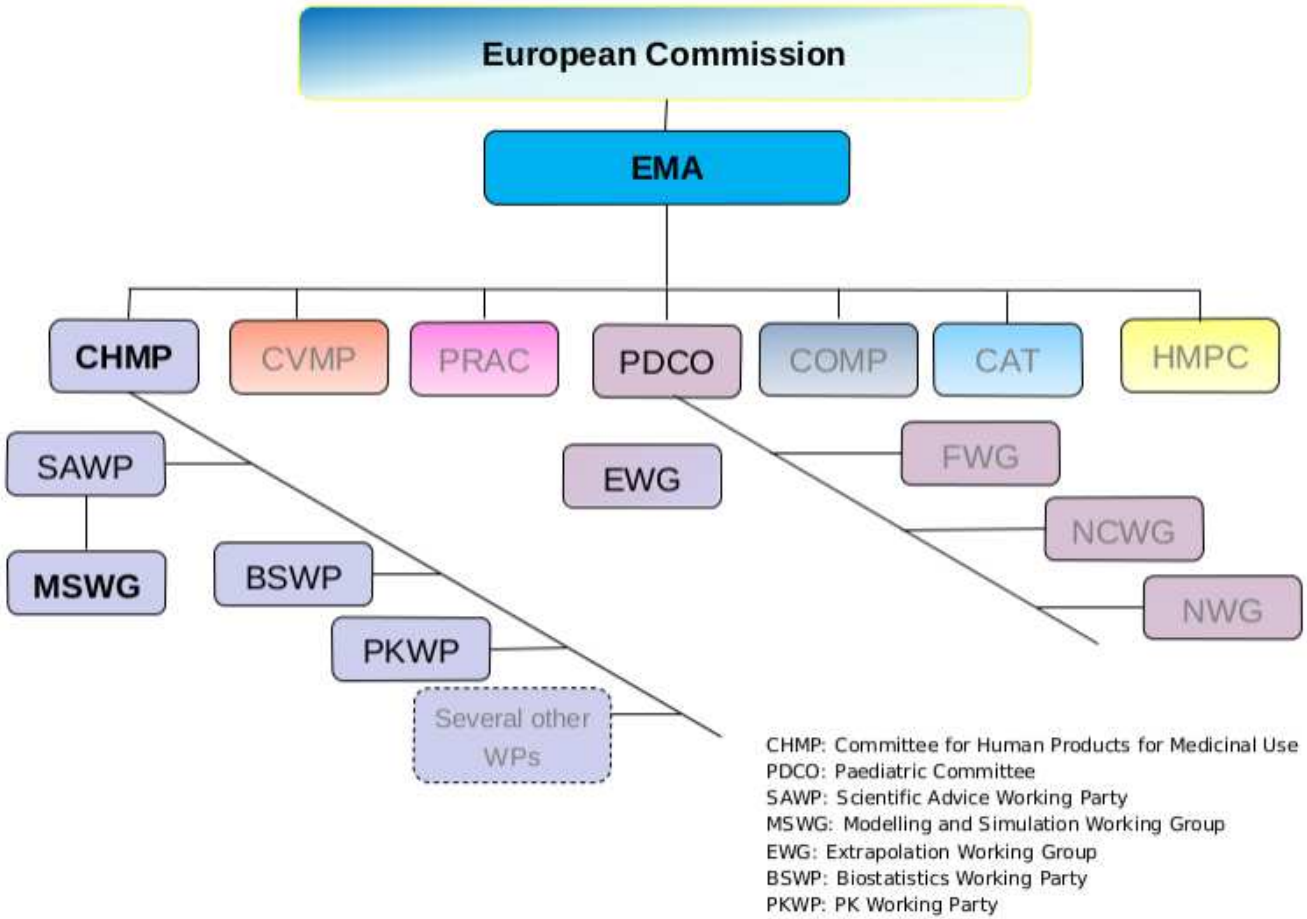

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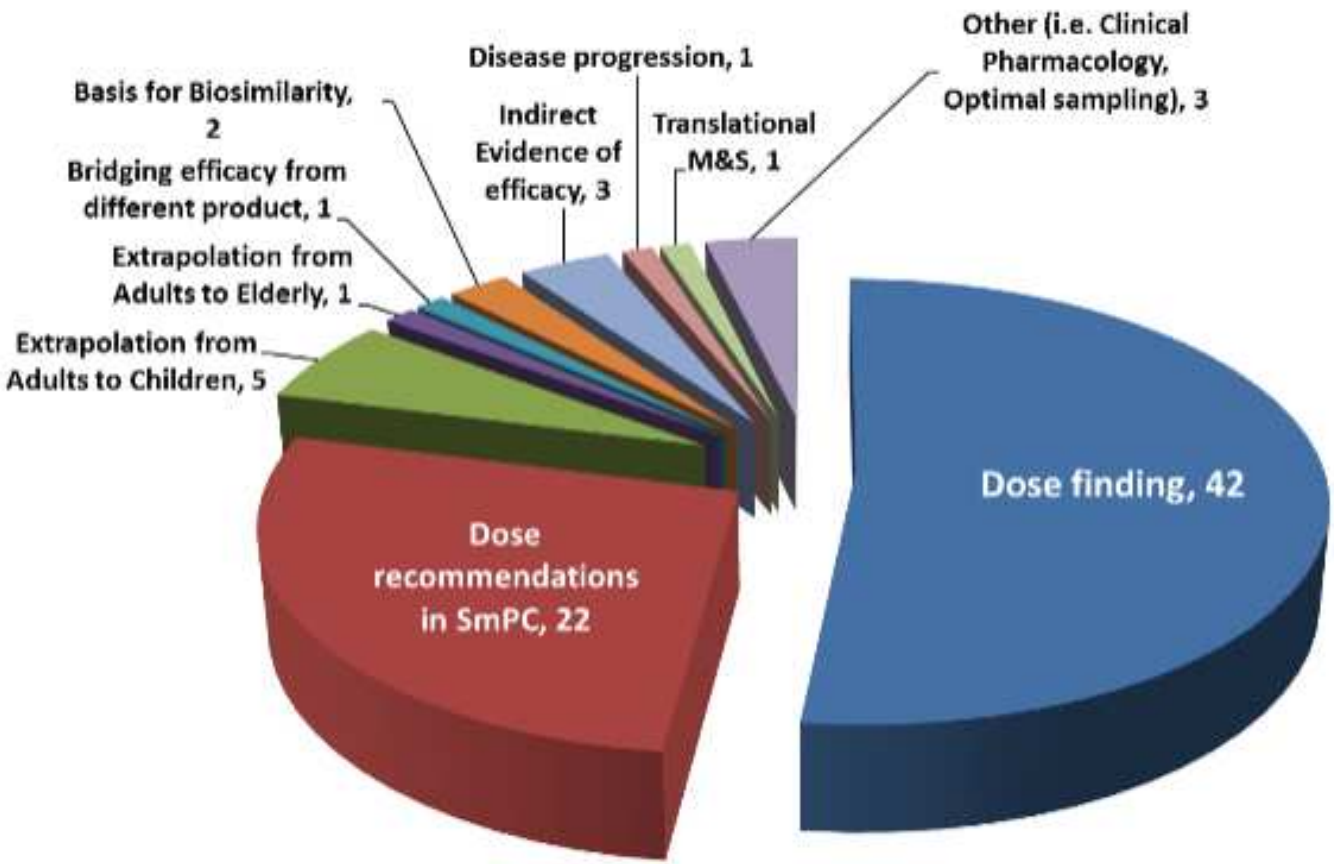

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Mots clés :	01/01/2000 - 31/01/2010	01/01/2004 - 31/01/2014
« Simulation » « clinical » « trial »	3477	4033
« Trial simulation »	61	70
« Clinical trial simulation »	48	55

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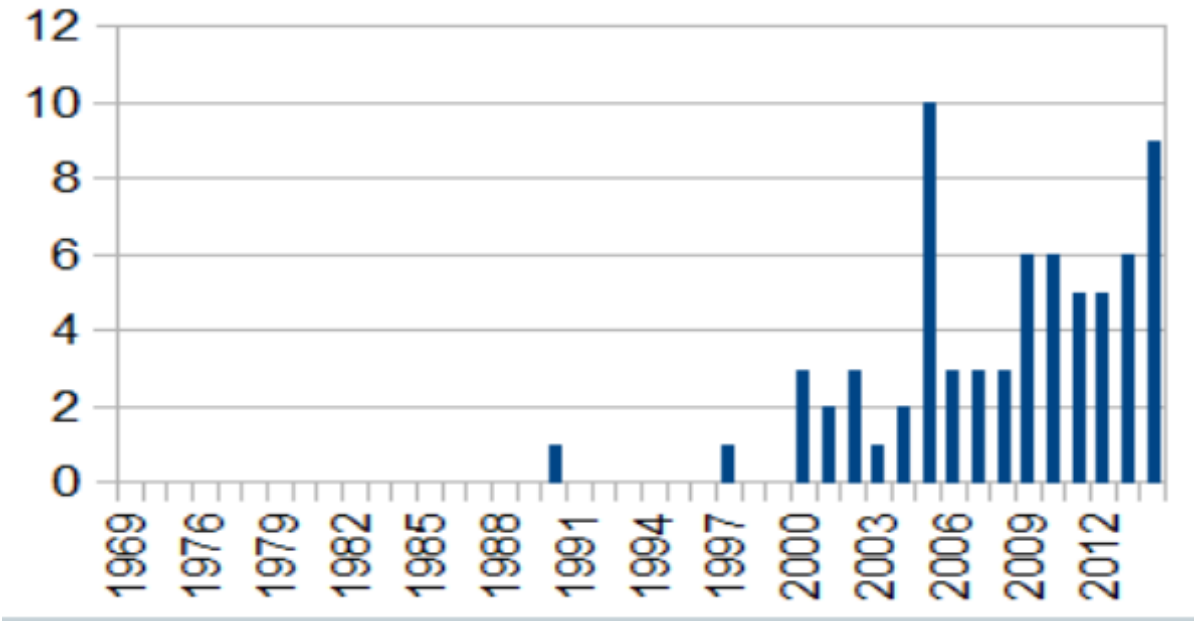

Nature of these articles

State of art	2	General discussion	6
Methodology	2	Methodology + case study	4
PK / PD	9	Sentivity analysis	3
"Real" simulated clinical trial	29		

Objectives of these articles

Primary objectives		Secondary objectives	
Virtual partients generation	9		
"Life of the trial"	12	Disease progression	4
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		Placebo evolution	7
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Patients	C^1	C^2	C^3	C^4	...	C^k
1	c_1^1	c_1^2	c_1^3	c_1^4	...	c_1^K
2	c_2^1	c_2^2	c_2^3	c_2^4	...	c_2^K
...	...	...	...	...	...	...
n	c_n^1	c_n^2	c_n^3	c_n^4	...	c_n^K

① **From Bibliography : purely Bayesian approach**

- Identify marginal distribution of each C^k
- Generate dataset from these distributions
- **Main issue :** to take into account correlation between covariates

Aim : Create a database of covariate values.

Patients	C^1	C^2	C^3	C^4	...	C^k
1	c_1^1	c_1^2	c_1^3	c_1^4	...	c_1^K
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n	c_n^1	c_n^2	c_n^3	c_n^4	...	c_n^K

① From Bibliography : purely Bayesian approach

- Identify marginal distribution of each C^k
- Generate dataset from these distributions
- **Main issue :** to take into account correlation between covariates

Crucial issue

Assume $X_1 \sim \mathcal{N}(\mu_1, \sigma_1)$ and $X_2 \sim \mathcal{N}(\mu_2, \sigma_2)$

Consider X_1 and X_2 correlated and $\rho = Corr(X_1, X_2)$

- Draw 1000 independant copies of (X_1, X_2)
- Construct
- Consider the 95% IC of Y : $[Y_{(250)}, Y_{(750)}]$
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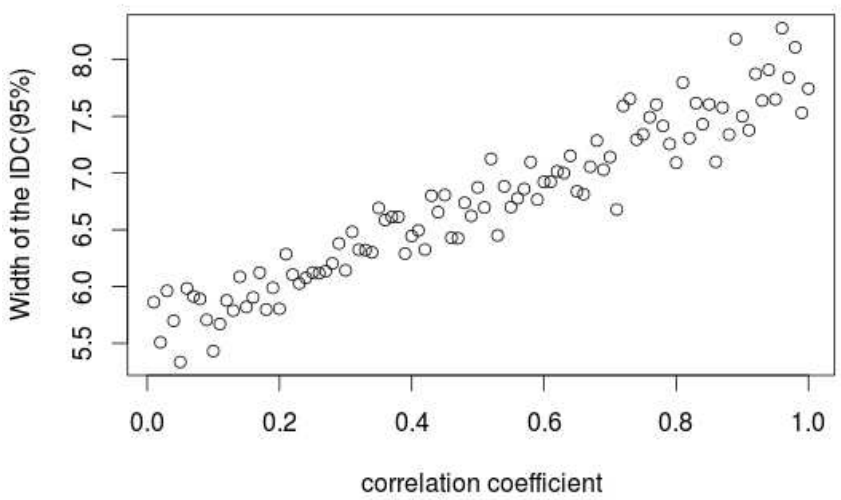

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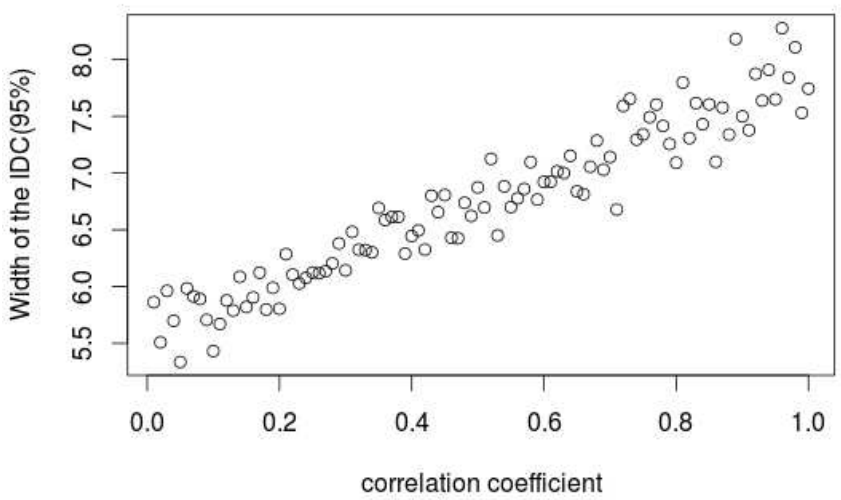

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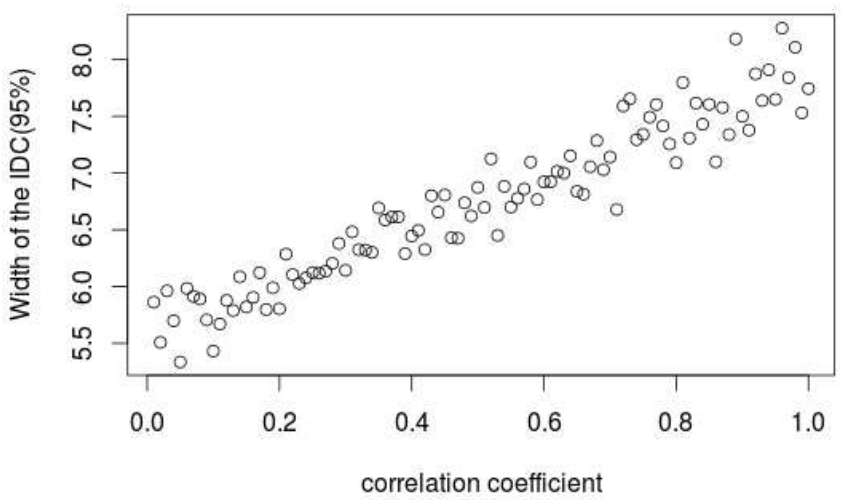

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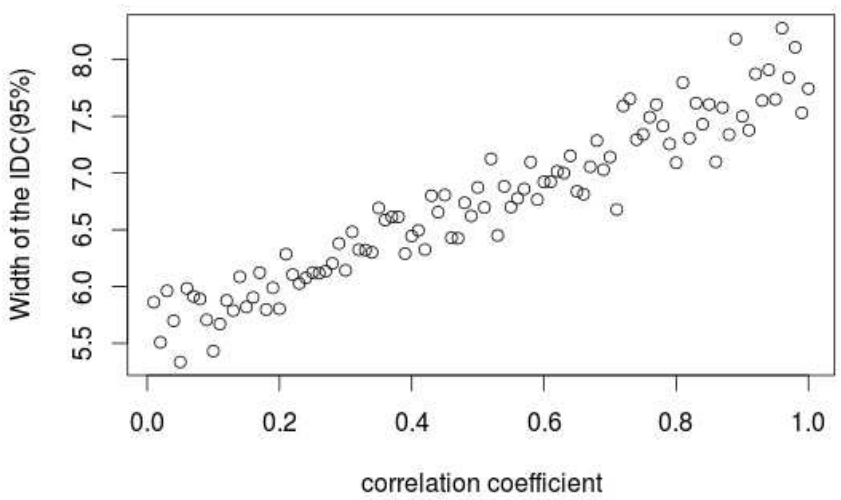

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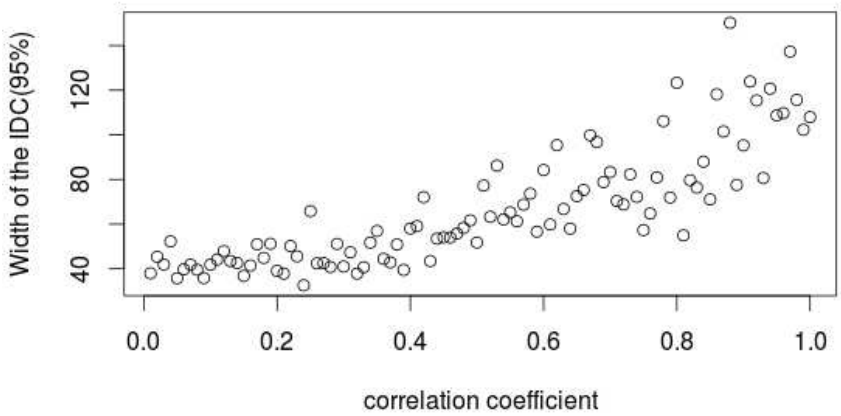

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Aim : to create a **realistic database** from this database.

- The links between covariates are (more or less) preserved

Notations : Denote $\vec{c}_i$ the vector of patient i covariates.

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- Continuous, in this case, one denotes it ${}^{c}C$
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- Draw $\vec{c}_i$ from the empirical distribution
  - **+ :** data are realistics
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    May be useful to validate a C.T. design but not to optimize it

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- Fit a distribution for the vector $(C^1, C^2, \ldots, C^k)$ from historical data.
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Problem : **How to fit such a distribution ?**

④ Multinormal Distribution

- If all the covariates are normaly distributed
- It is enough to estimate the mean vector and the variance-covariance matrix
- In most real setting it is a mixed of continuous and categorical distributions

Remark

Problem can be split in groups of independants covariates

$(C^1, \ldots, C^L)$ *independant of* $(C^{L+1}, \ldots, C^K) \Longleftrightarrow f_{(C^1,\ldots,C^K)} = f_{(C^1,\ldots,C^L)} \times f_{(C^{L+1},\ldots,C^K)}$

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Idea :

Use **conditional distribution** to separate continuous and categorical covariates

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Estimation step :

- Fit the distribution of $({}^dC^{L+1},\ldots,{}^dC^K)$
- For each configuration $({}^dC^{L+1},\ldots,{}^dC^K)$ fit the distribution of

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Assume an HD of 500 patients. The covariates of interest are :

- Sexe (categorical 2 modalities).
- Age (continuous).
- Smoke (categorical 2 modalities (Yes / No)).

Estimation step :

1. "Fit" the distribution of (Sexe,Smoke)
   - Compute the proportion of each modality
2. "Fit" the conditional distribution of Age knowing (Sex,Smoke)
   - Estimate mean and variance under normality assumption

Estimation step : to create SD repeat 500 times :

- Draw (Sexe,Smoke) according to ❶
- Draw Age according to ❷

Remark

- ***4*** *estimations to estimate the proportions of each of the 4 configurations*
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Total : 12 *estimations*

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- Weight (continuous)
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- Cholesterol (continuous)
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- S-BP (continuous)
- Sex (categorical 2 modalities)
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Remark

1. - ***24*** *estimations to estimate the proportions of each of the 24 configurations*
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   Total : 72 *estimations*
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⑥ Continuous Method

Idea :

Consider all the covariates as continuously distributed (normally or log-normally)

Estimation step :

- Estimate the means vector $\vec{\mu}$ and the variance-covariance matrix Σ from the Historical Database

Simulation step :

- Draw n values $((u_i^1, \ldots, u_i^K)_{i=1,\ldots,n}$ from the multinormal distribution $\mathcal{N}(\vec{\mu}, \Sigma)$
  - For a **continuous covariate** : finished ${}^c c^k = u^k$ for $k = 1, \ldots, L$
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$$CrV_m^k = \mu_k + \Sigma_{k,k}\phi^{-1}(\sum_{i=1}^{m} p_i), \qquad 1 \leq m \leq M$$

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  - For a **continuous covariate** : finished ${}^c c^k = u^k$ for $k = 1, \ldots, L$
  - For a **categorical covariate with M modalities** ${}^d C^k$: make use of critical values

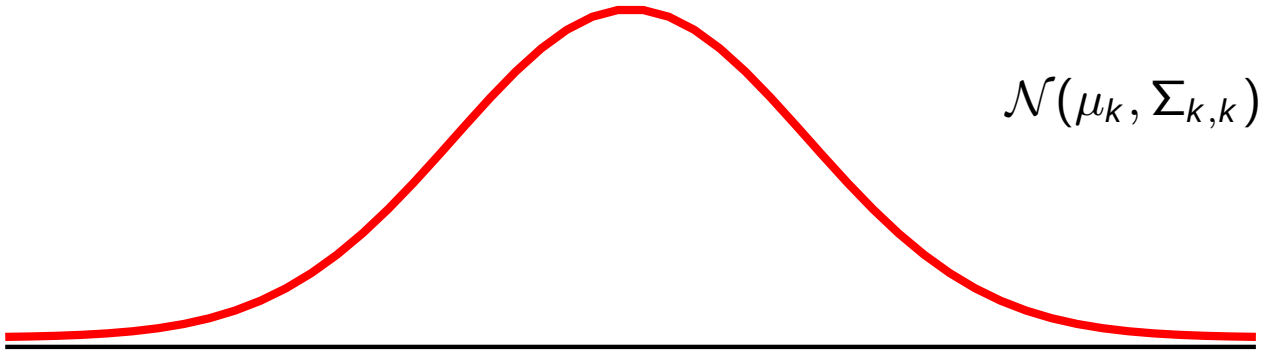
$$CrV_m^k = \mu_k + \Sigma_{k,k}\phi^{-1}(\sum_{i=1}^{m} p_i), \qquad 1 \leq m \leq M$$

where

- $(p_m;\ 1 \leq m \leq M)$ the proportions of each modality estimated from H.D.
- μ_k and $\Sigma_{k,k}$ the parameters of the normal distribution fitted from H.D.
- ϕ denote the standard normal distribution.

Assume M equal to 3 modalities.

Modality	${}^dC^k = 1$	${}^dC^k = 2$	${}^dC^k = 3$
Proportion	p_1	p_2	p_3



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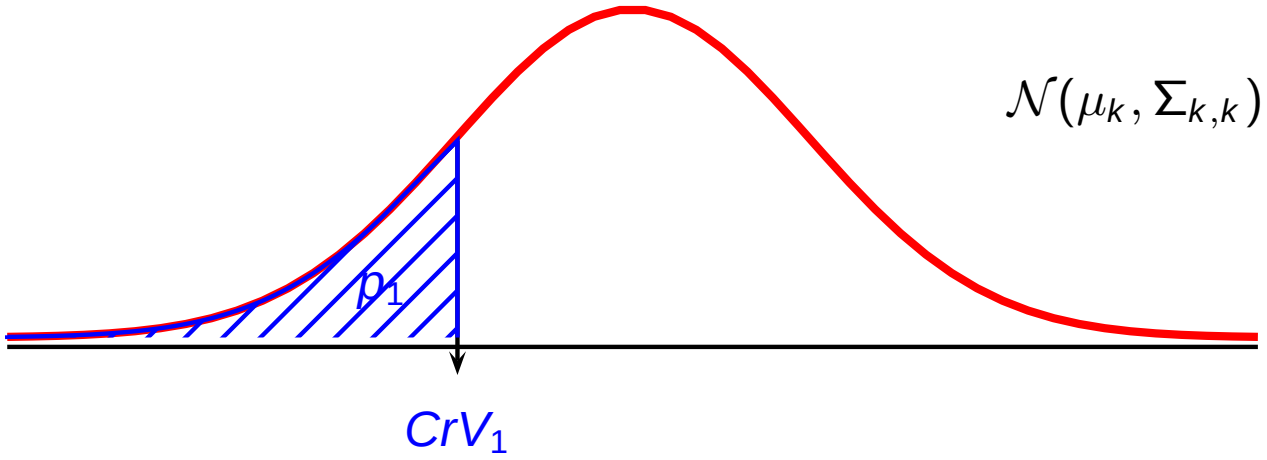

For patient i, we have

$$-\infty < u_i^k \leq CrV_1^k \qquad \text{then} \quad {}^{d}C_i^k := 1$$

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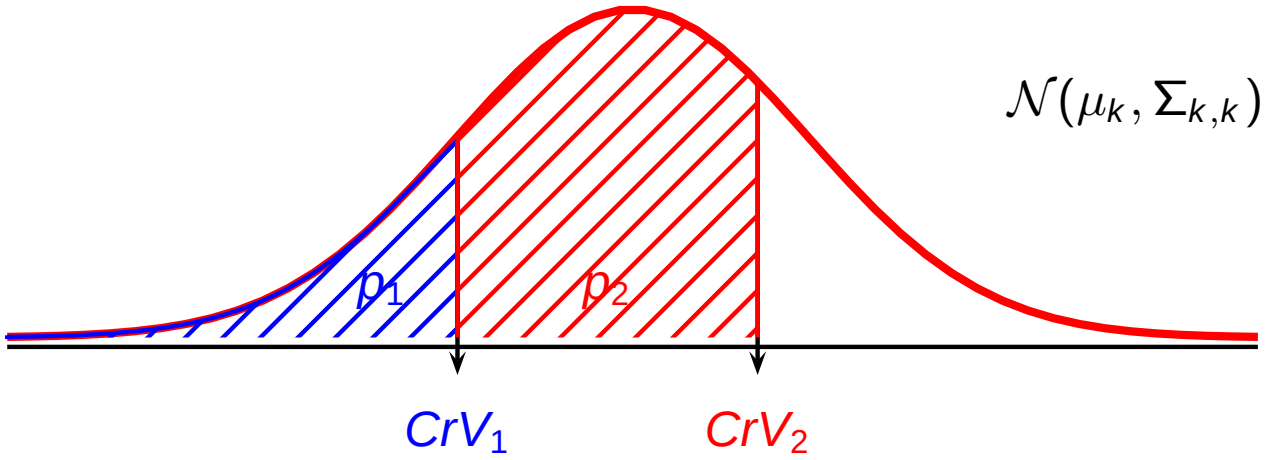

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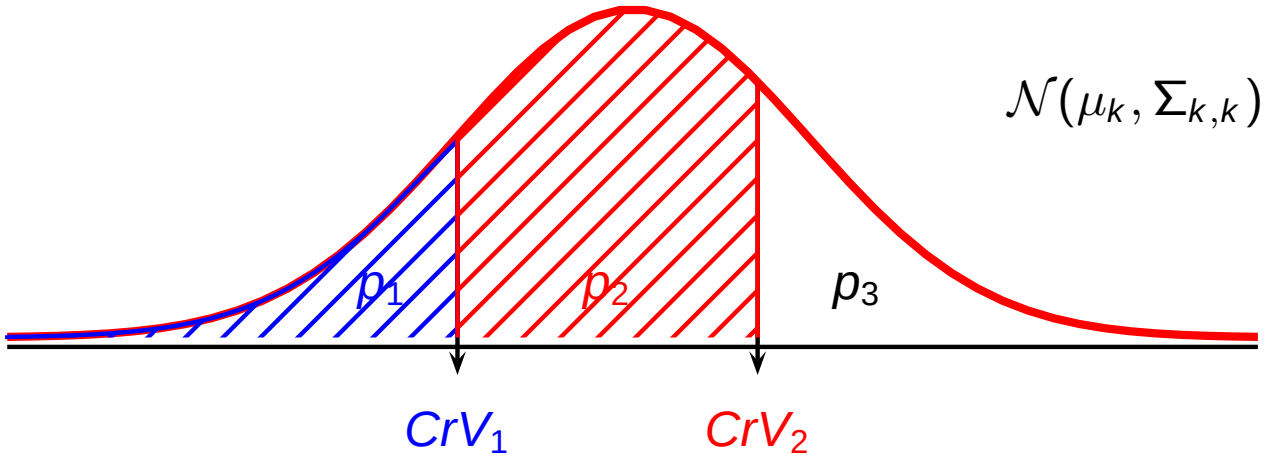

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$$CrV_2^k < u_i^k \leq +\infty \quad \text{then} \quad {}^dC_i^k := 3$$

Simulation study in Tannenbaum *et al*.

- **1 categorical** distribution with 2 modalities
- **2 continuous** distributions CONT1 and CONT2 log-normaly distributed

Parameter	CONT1			CONT2
Mean (CAT = 1)	10	50	90	90
Mean (CAT = 2)	100			100
Mode ratio	0.1	0.5	0.9	0.9
CV (%)	30			30
Minimum	0			0
Maximum	1000			1000

- Parameters of the simulation scenarios

Parameter	values		
Mode ratio	0.1	0.5	0.9
CORR between CONT1 and CONT2	0	0.45	0.9
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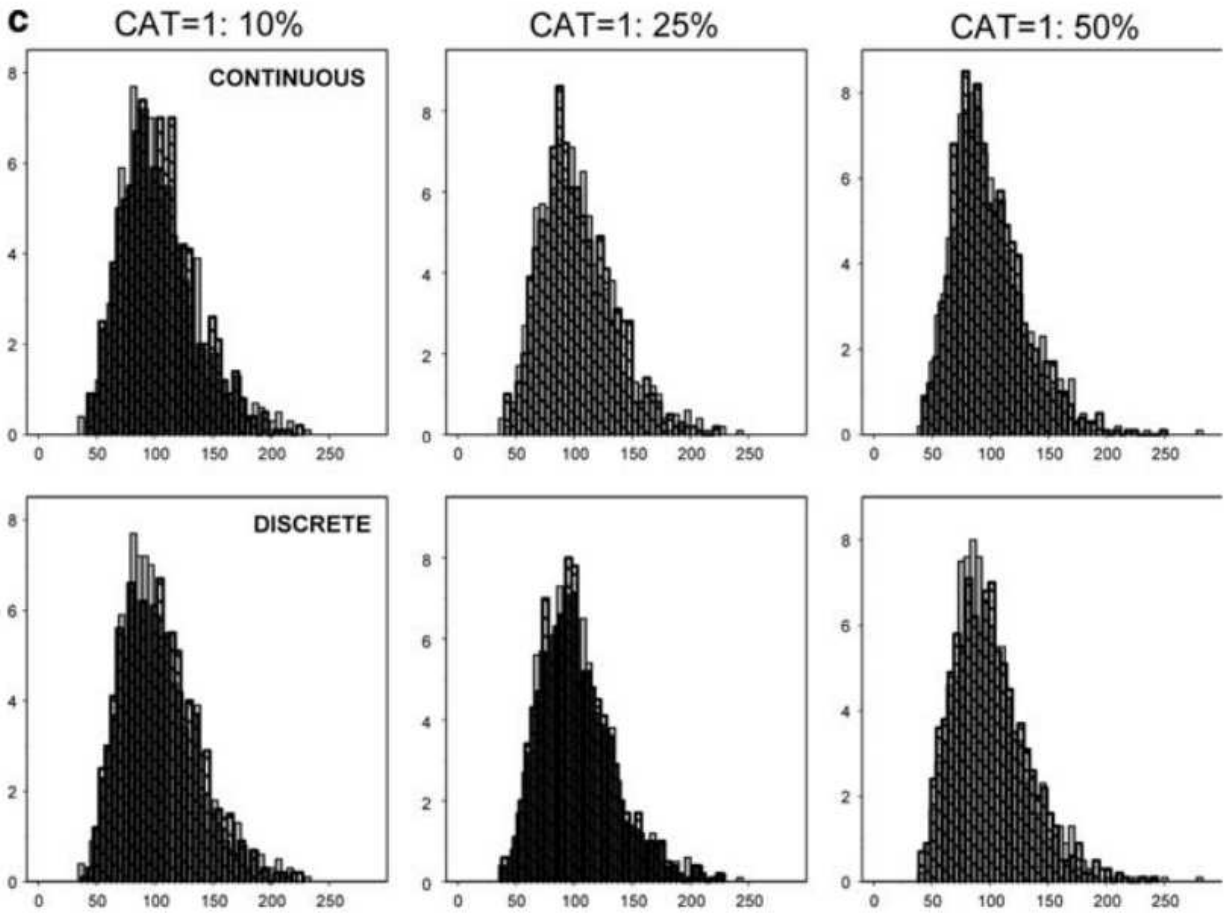

FIGURE: Marginal distribution of CONT1 for $MR = 0.9$ and $R = 0$

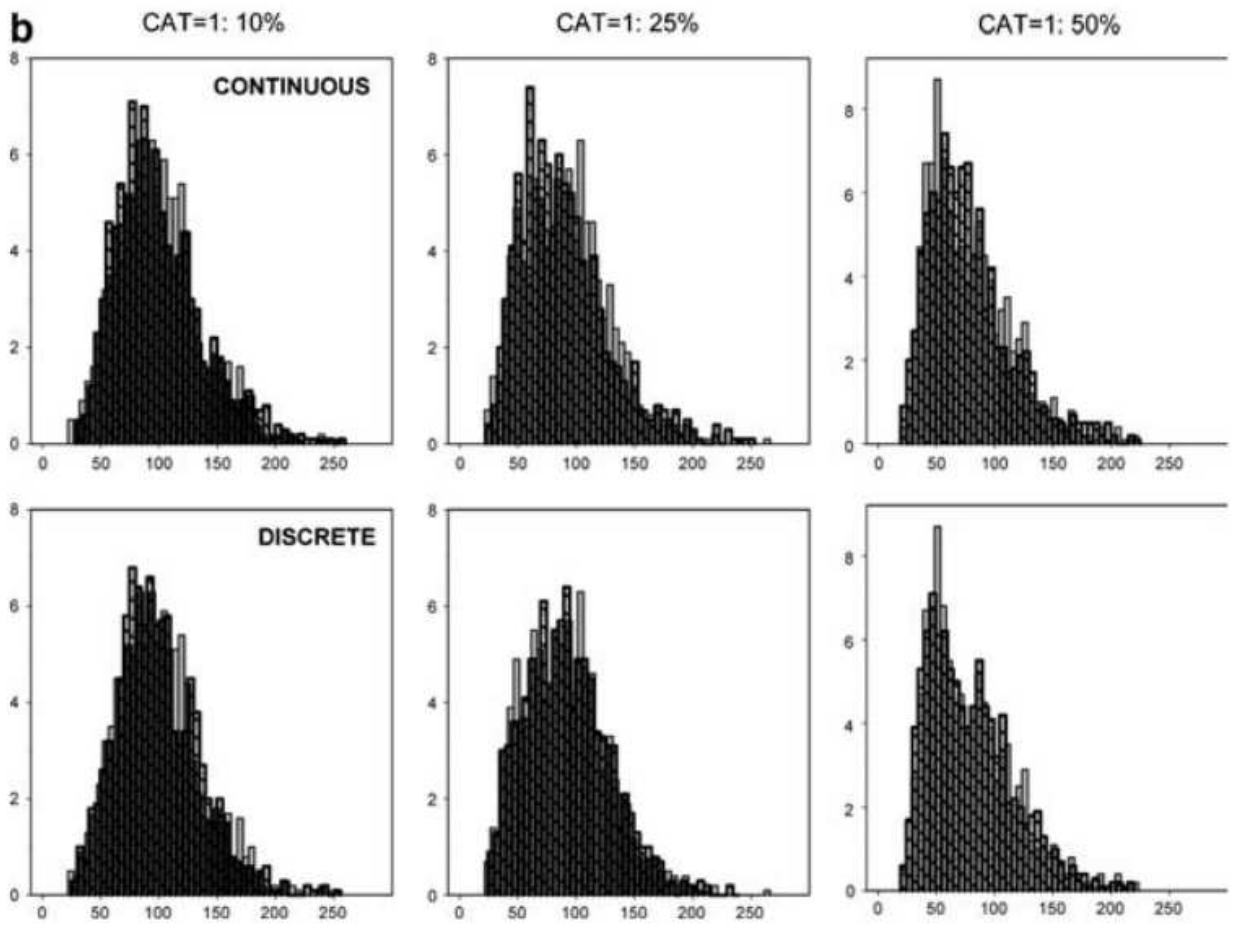

FIGURE: Marginal distribution of CONT1 for $MR = 0.5$ and $R = 0$

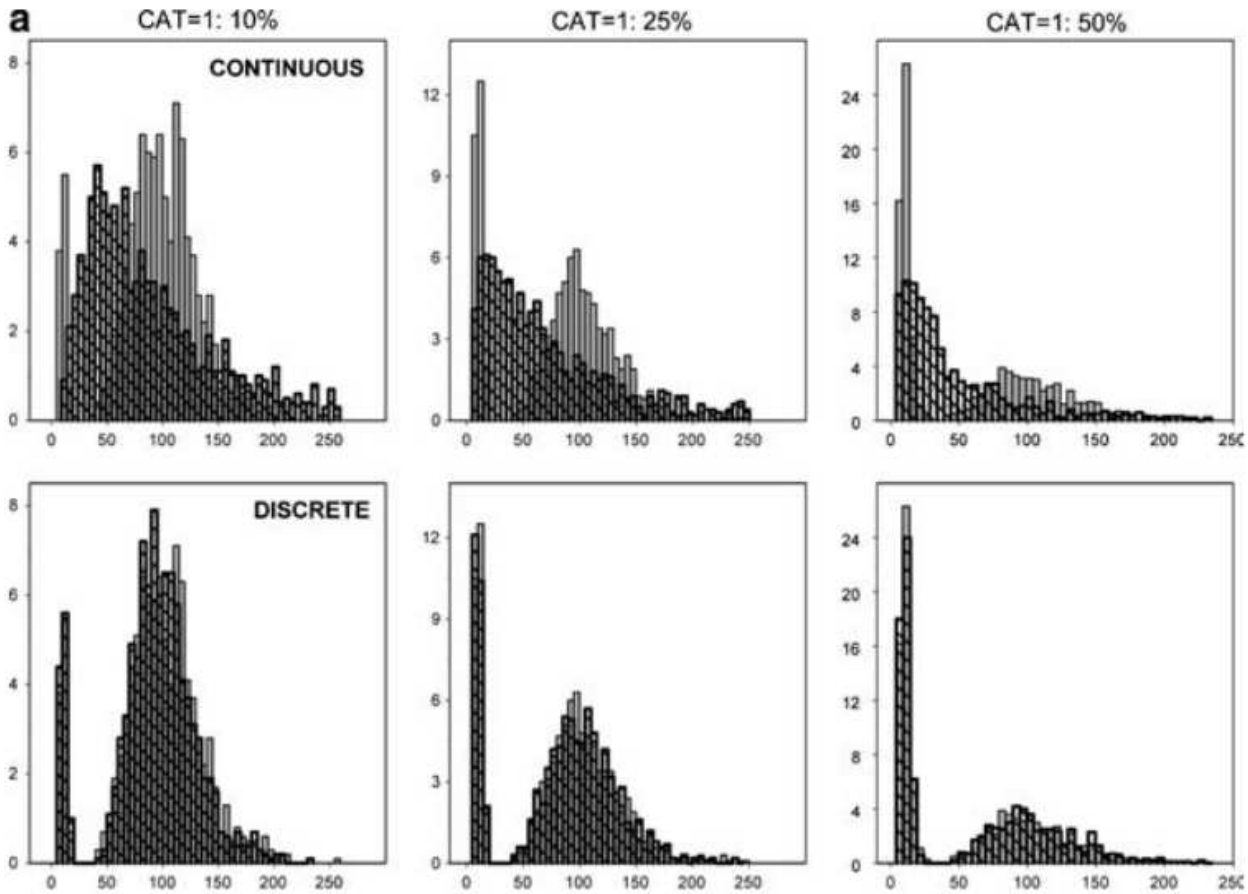

FIGURE: Marginal distribution of CONT1 for $MR = 0.1$ and $R = 0$

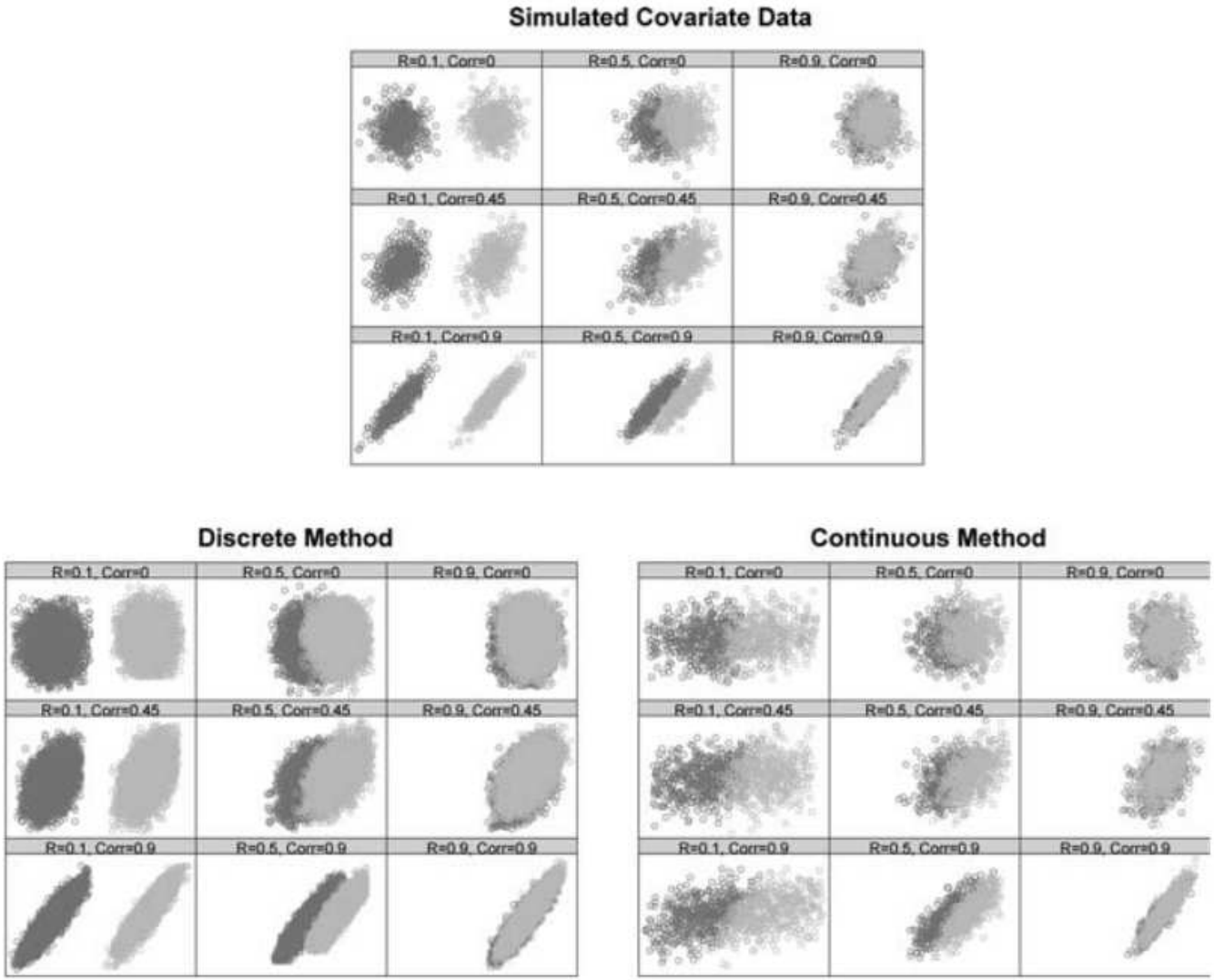

FIGURE: Correlation between CONT1 and CONT2 with 50% of patients in each subgroup

Thank you for your attention...

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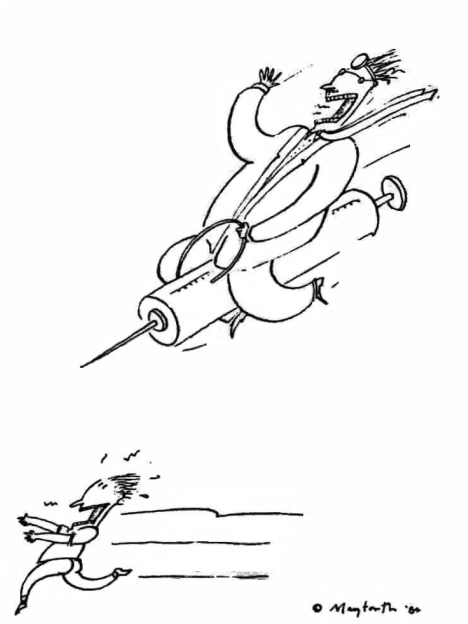

Do not be scared,

It is a SCT ...