NHS National Institute for Health Research

NIHR Statistical Meeting
13th February 2012

KING'S College LONDON

Sample Size by design in complex intervention trials

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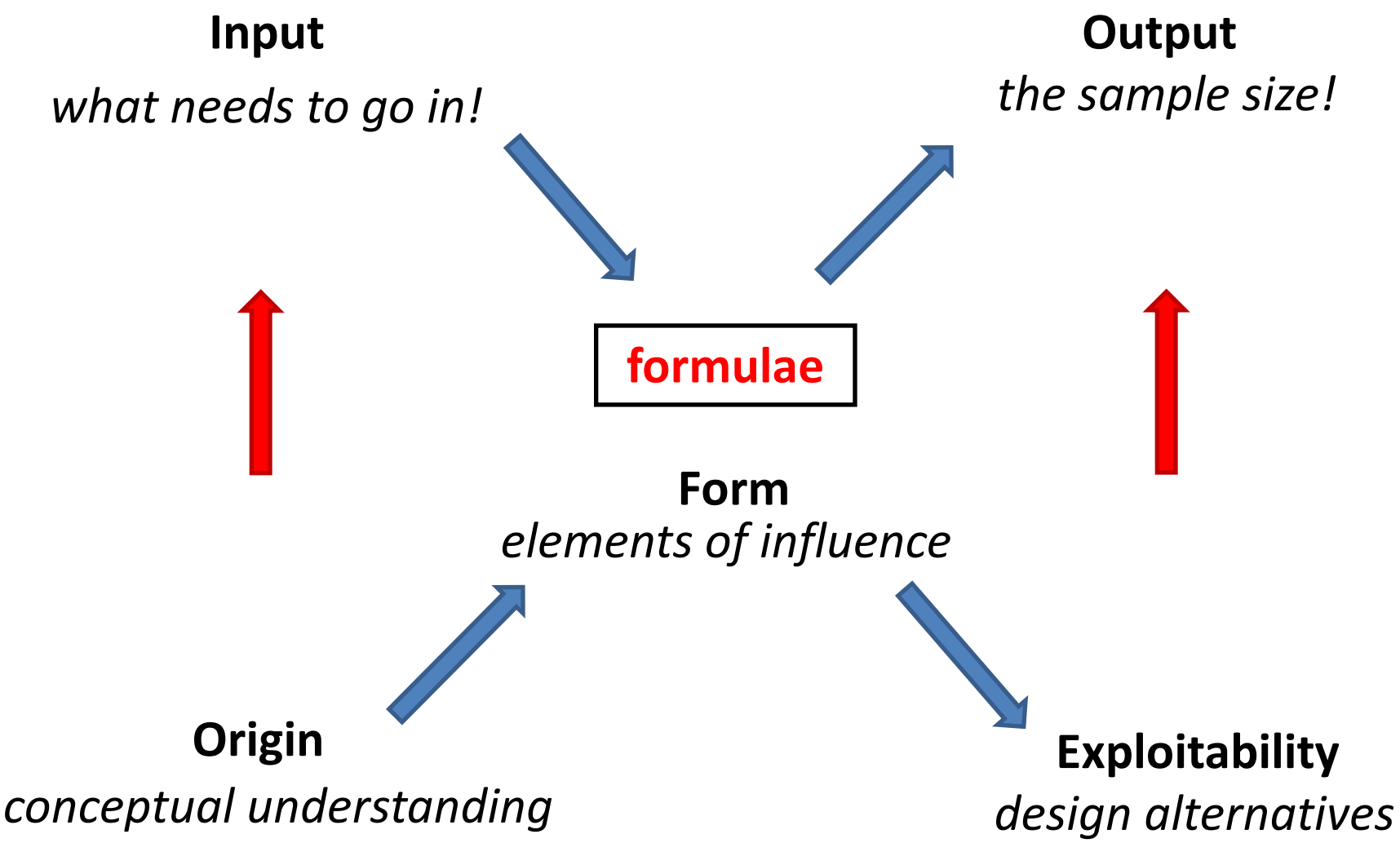
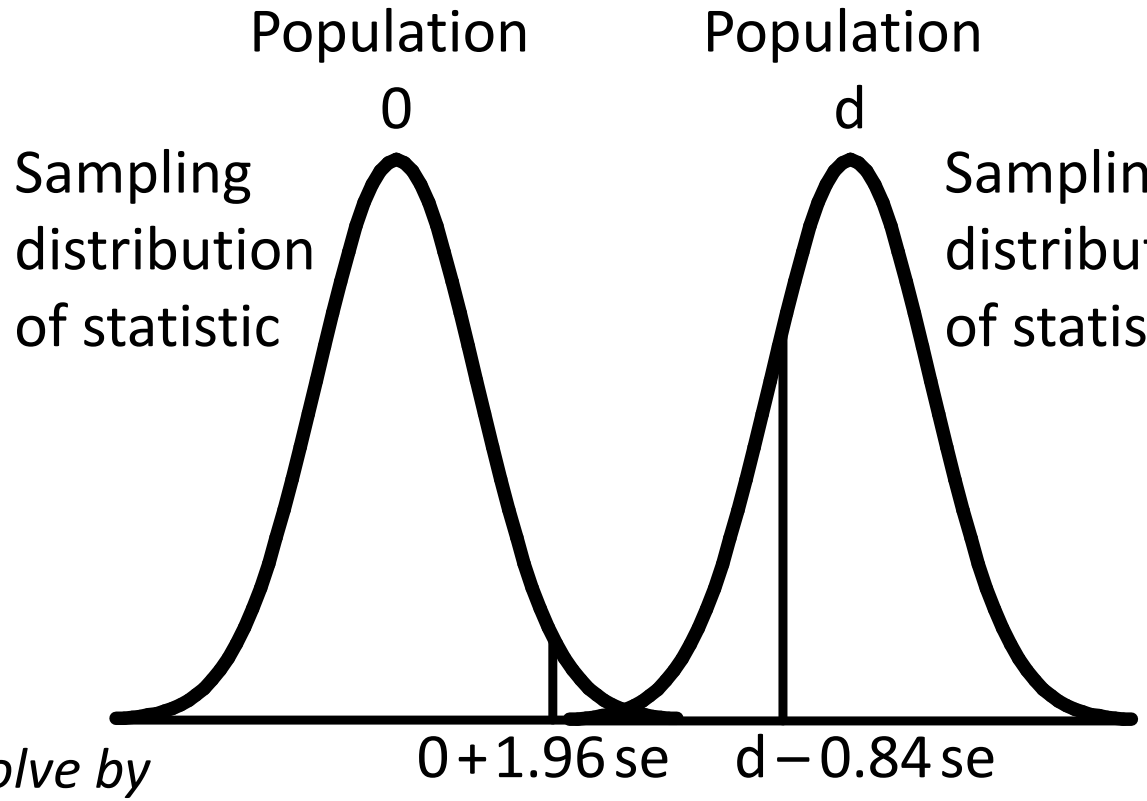
What can sample size formulae tell us?

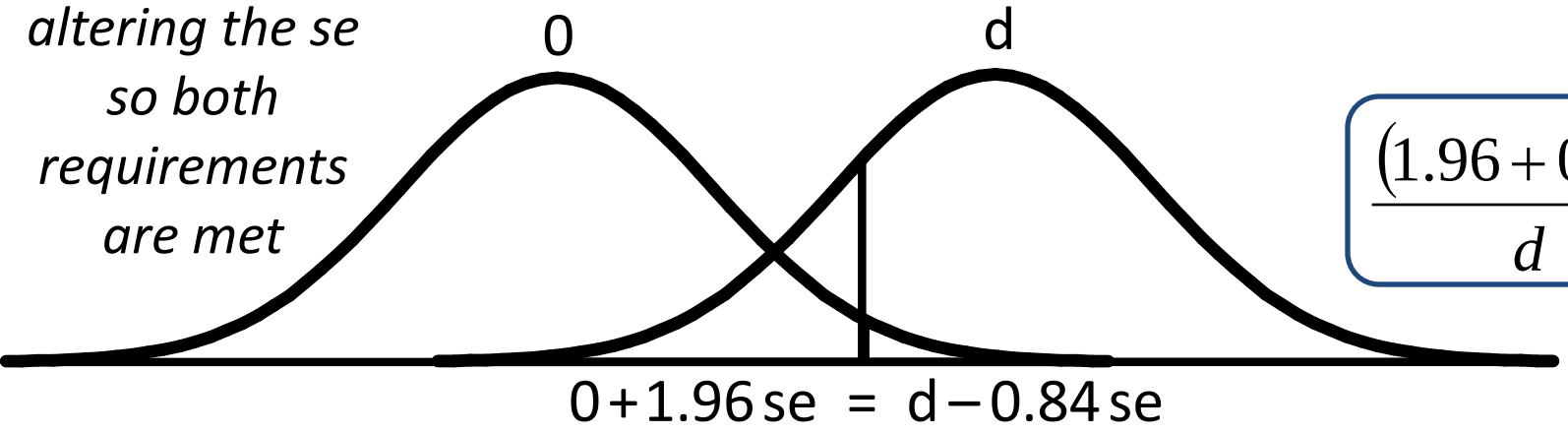


Formulae remind us – origins, concepts, understanding



Sampling Variability
Distributions
Normality
CLT
Estimates
Standard Error
Critical values
Powerful tests
Decisions

Resolve by altering the se so both requirements are met



$$\frac{(1.96+0.84)}{d}se = 1$$

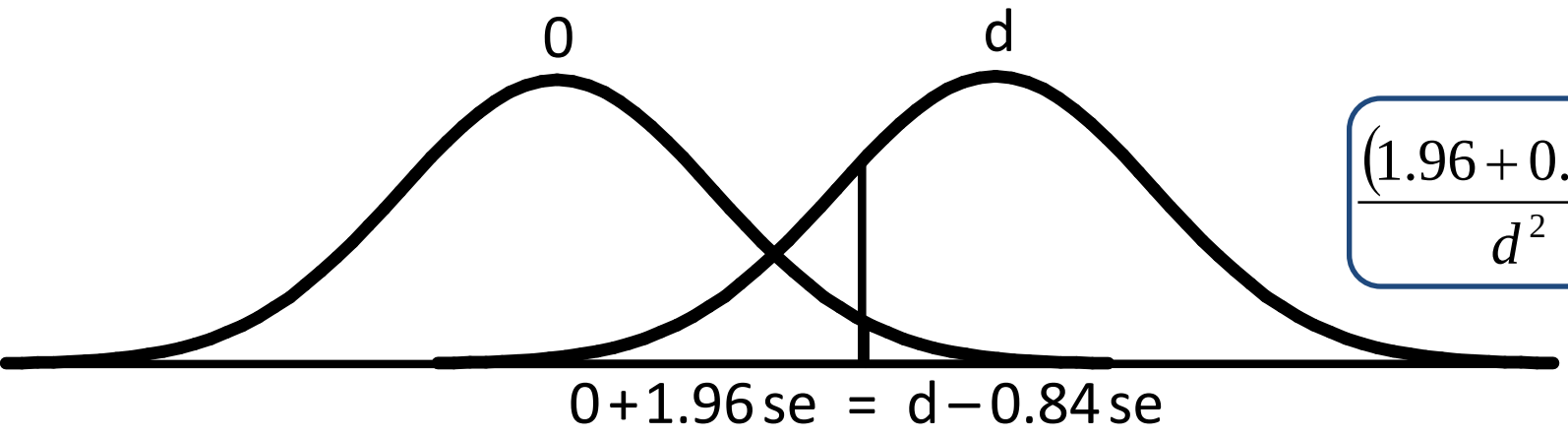
Comparing formulae - shows cost to se^2 of sub/groups

Mean/proportion; 1 group $$se^2 = sd^2\left[\frac{1}{n}\right] \qquad se = \frac{sd}{\sqrt{n}}$$

Difference; 2 groups (n per group) $$se^2 = sd^2\left[\frac{1}{n}+\frac{1}{n}\right] \qquad se = \sqrt{2}\,\frac{sd}{\sqrt{n}}$$

Difference in difference (Subgroup; interaction) $$se^2 = sd^2\left[\frac{1}{\frac{1}{2}n}+\frac{1}{\frac{1}{2}n}+\frac{1}{\frac{1}{2}n}+\frac{1}{\frac{1}{2}n}\right] \qquad se = \sqrt{8}\,\frac{sd}{\sqrt{n}}$$

Subgroup – assessed with test for interaction – detected with factorial design



$$\frac{(1.96+0.84)^2}{d^2}\,se^2 = 1$$

Factorial Design – two interventions/factors

- to test for ***interaction*** – needs the much larger size
- mainly used for ***efficiency*** – *buy 1 get 1 free*
  - estimate 1 factor combined over *levels* of the other

Montgomery AA, Astin AP, Peters TJ *Reporting of factorial trials of* ***complex interventions*** *in community settings: a systematic review.* Trials 2011;12:179

*~ 70% (38/53) based sample size on analysis "**at the margins**"*

- assumes no [population] interaction between interventions

A *sample* may provide very different intervention effect estimates at each level of the other factor "***inside the table***"

2 x 2 factorial example: Dunger et al. BMC Paediatrics 2009;9:79

Adolescent Type 1 Diabetes Cardio-Renal Intervention Trial

Allocation	No Statin	Statin	Ace factorial
No Ace	**125** **Neither**	**125** **Statin only**	250
Ace	**125** **Ace only**	**125** **Both**	250
Statin factorial	250	250	**500**

Outcome = log Albumin Creatinine Ratio (ACR); interpreted in geometric means

93% power to detect "***in the margin***" 25% reduction in ACR.

Sensitivity: 82% power to detect "***inside the table***" 30% reduction

Uses alternatives for ***power*** and "***d***"

Provides for consequence of interaction or chance

Choosing "*d*" - the detectable effect size

Consort on sample size:

- a balance between ***medical and statistical*** considerations
- large enough to detect a difference ***deemed clinically important*** with high power, if such a difference exists
- ***SD*** is an element of the calculation

Don't nominate/calculate a "d" that you alone consider important

Do ask questions to establish "worthwhile" and "plausible" ranges

Do ask for relevant good quality evidence (for "d" and sd)

Avoid side-stepping with Cohen's effect size

Cohen's effect size

$$= \frac{d}{sd}$$

Choices:

0.2 → "Small"
0.5 → "Medium"
0.8 → "Large"

- hides importance of 'd'
- Hides SD raised from measurement error

Explore longer recruitment, extra centre(s), design options b4 ***d***

Formulae have common form - with a design constant

Mean/proportion; 1 group $se^2 = 1 \bullet \frac{sd^2}{n}$

Difference; 2 groups $se^2 = 2 \bullet \frac{sd^2}{n}$

Difference in difference (Subgroup; interaction) $se^2 = 8 \bullet \frac{sd^2}{n}$

Difference; 2 unequal groups (in a:1 ratio) $se^2 = 2\frac{(a+1)^2}{4a} \bullet \frac{sd^2}{n}$

3:1 (**a=3**)
increases by 1/3

14:1 (**a=14**)
equates to
test for interaction

Elements of se^2

Outcome variability

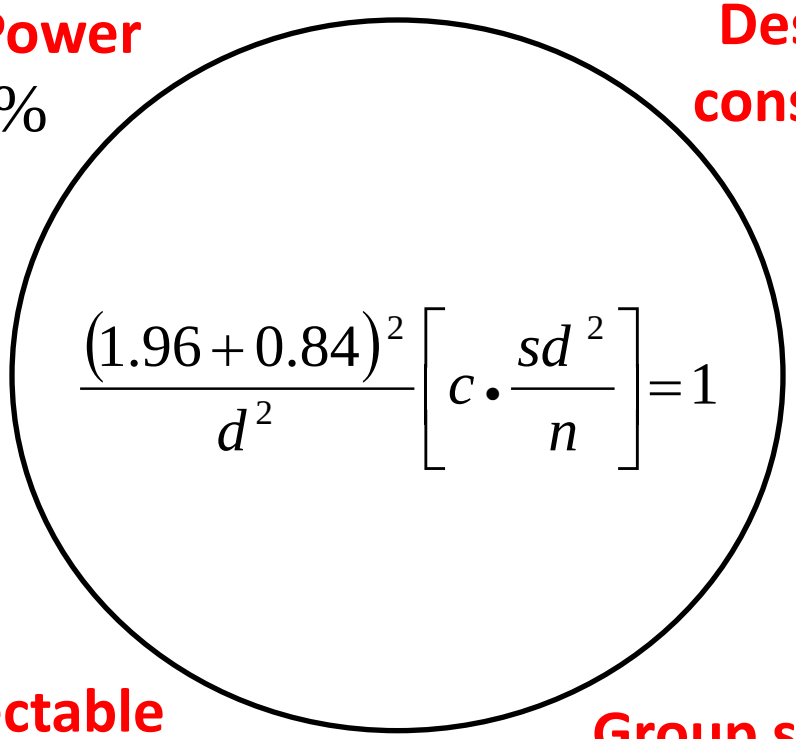
$$se^2 = c \bullet \frac{sd^2}{n}$$

Design constant

Group size

$$\frac{(1.96+0.84)^2}{d^2} se^2 = 1$$

Balancing the elements of influence



Power

$90\% \leftrightarrow 80\%$

Design constant

$a = 3 \leftrightarrow a = 1$

Significance level

fixed

$$\frac{(1.96+0.84)^2}{d^2}\left[c \bullet \frac{sd^2}{n}\right]=1$$

Outcome variability

Adjust for baseline

$$sd^2 \rightarrow sd^2\left(1-r^2\right)$$

r = 0.5

Detectable effect size

Group size

- Power / Adjusted SD offer <u>some</u> (25%) flexibility
- Though "***n***" is the <u>main</u> 'purchaser' of "***d***"
- *NB: Design constant can have appreciable effect*

Compare designs: ratio of sampling variances = design effect

Mean/proportion; 1 group $se^2 = 1 \bullet \frac{sd^2}{n}$ **(2)**

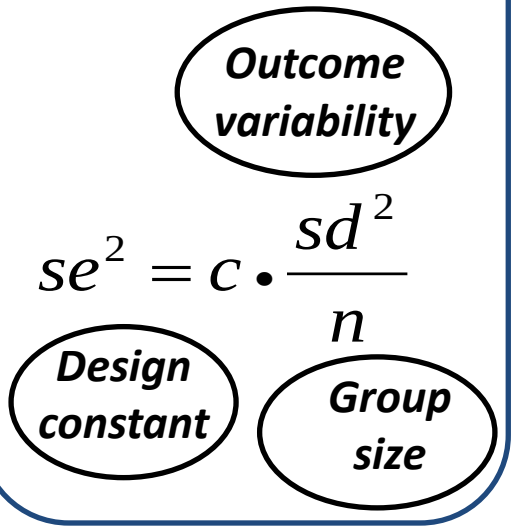
$$\frac{(1.96+0.84)^2}{d^2} se^2 = 1$$

Difference; 2 groups $se^2 = 2 \bullet \frac{sd^2}{n}$

Difference in difference (Subgroup; interaction) $se^2 = 8 \bullet \frac{sd^2}{n}$

Difference; 2 unequal groups (in a:1 ratio) $se^2 = 2\frac{(a+1)^2}{4a} \bullet \frac{sd^2}{n}$

Elements of se^2



Clusters of size *m*; 1 group
Intracluster correlation ρ $se^2 = [1+(m-1)\rho] \bullet \frac{sd^2}{n}$ **(1)**

Clustering introduces an unknown design constant

Design Effect = **(1) / (2)**
(**Kish**, 1951)

$$deff = 1+(m-1)\rho$$

Design effects (*deff*) due to clustering in surveys and trials

cluster mean

Single cluster of m subjects

$$se^2 = \frac{1}{m^2} V\left(y_1 + y_2 + \ldots y_m\right)$$

$$= \frac{1}{m^2}\left[m\, sd^2 + \binom{m}{2} 2\rho\, sd^2 \right]$$
$$\text{Cov}$$

$$= \frac{sd^2}{m}\underbrace{\left[1+(m-1)\rho\right]}_{deff}$$

survey mean

k independent clusters (n=km)

$$se^2 = \frac{sd^2}{n}\underbrace{\left[1+(m-1)\rho\right]}_{deff}$$

difference in trial means

2 groups each of k clusters

$$se^2 = 2\frac{sd^2}{n}\underbrace{\left[1+(m-1)\rho\right]}_{deff}$$

Inflate ***n*** from simple design by ***deff*** by inflating ***k*** (clusters) not ***m*** (size).

Inflating ***m*** increases the ***deff*** itself, further increasing ***m***, ***deff***, ***m***, ***deff*** …

complex intervention trial

with only 1 group clustered

$$se^2 = \frac{sd^2}{n} + \frac{sd^2}{n}\left[1+(m-1)\rho\right]$$

Campbell MJ *Stat Meth Med Res* 2000;9:81-94 **-** Cluster RCTs in general practice research

Eldridge S, Ashby D, Kerry S *Int J of Epi* 2006;35:1292-1300 – clusters of unequal size

What is the influence of this Design effect (*deff*)?

$$deff = 1 + (m-1)\rho$$ (product form)

ρ is fortunately typically...

- ***large*** when m is naturally ***small***
  "close-knit" - e.g. **household**

  see *m = 1.2 deff ≤ m bounded!*

- ***small*** when m is naturally ***large***
  e.g. **regions**

- **intermediate** (0.01 to 0.05)
  in **School Classes**, **General Practices**

  m=21, ρ=0.01 → *deff*=1.2
  ρ=0.05 → *deff=2* *double!*

It may be more efficient...

- to use **more clusters**
  with **reduced *m***
  via shorter recruitment time
  or subsample within cluster
  (depends on costs etc etc)

- to **avoid clustered design**, if possible,
  accepting probably relatively small
  bias from ***contamination (arguably!)***

Torgerson DJ *BMJ* 2001;322:355 - Cluster randomisation answers contamination?
Okoumunne OC, Gulliford MC et al *HTA* 1999;3:5 - evaluating area-wide interventions

Imprecision in variance estimates: '*impact*' on SS & analysis

sd^2: 95% CI by study size

n	95% CI Rel. to estimate
20	0.55 to 2.00
30	0.60 to 1.75
50	0.70 to 1.50
100	**0.75 to 1.33**
250	0.85 to 1.20

ρ: Upper 5% Confidence limit

For sample sizes of ***km***=200

k *clusters*	*of size* ***m***	Upper 5% CI with $\hat{\rho} = 0.01$
40	5	0.11
20	10	0.10
8	25	0.11
4	50	0.19

Estimated ← Applies backwards

Anticipated → Applies forwards

Use ***previous*** $\hat{\rho}$ based on many clusters/studies

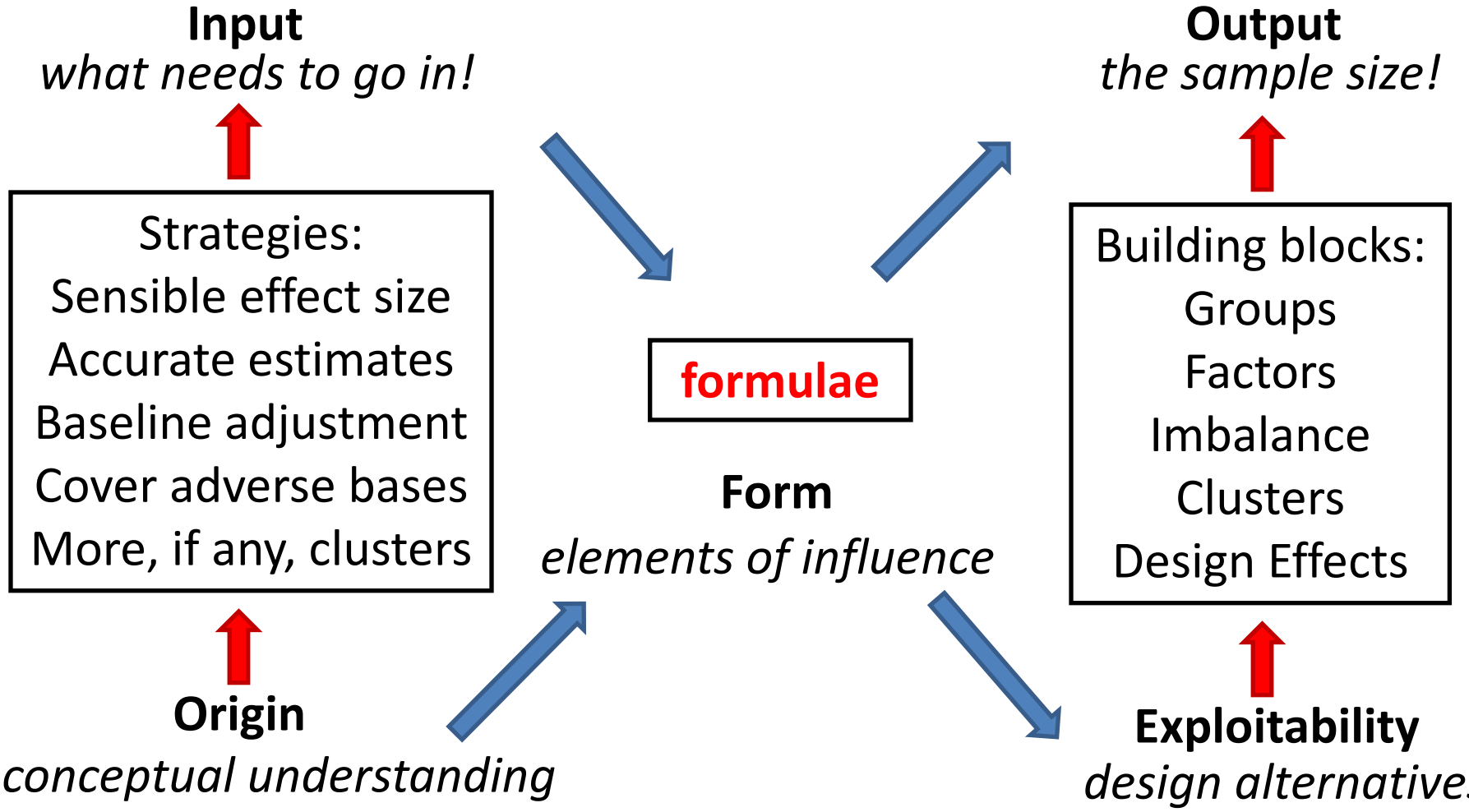
Reduce ***deff*** with reduced size clusters

Reduce '***impact***' by recruiting more clusters

Vickers AJ *Journal of Clin Epi* 2003;56:717-20 – The SD & Underpowering in RCTs

Turner R, Prevost AT, Thompson SG Allowing for imprecision of the intracluster correlation coefficient in the design of cluster RCTs *Stat Med* 2004;23:1195-1214

Sample Size by design - formulae inform better inputs



Donner A, Klar N (2000) Design & analysis of Cluster RCTs in health research, Arnold.
Julious SA (2009) Sample Sizes for Clinical Trials, CRC Press.
Bland JM The tyranny of power: ...a better way to calculate SS? *BMJ* 2009;339:b3985

@RSS on 26th March: Factorial / Two-stage / Stepped Wedge designs: why choose?