Introducing the adaptive platform design

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No relevant disclosures for this presentation
double Dutch
noun  [mass noun]

1  Brit. informal language that is impossible to understand; gibberish
Challenges in the ICU

- Multidisciplinary teamwork
- Continuity of 24/7 care
- Rapidly transforming environment
- Translation and implementation of evidence from research
- Individualisation of treatment
User-centered, Research-based Design of Futuristic Intensive Care Units

CARLOS MONTANA, HOYOS, STEPHEN TRATNEN, BALAJI BIRJANDI, BLAKE REMY, HUGH STEHUL, AND FRANK VAN HAREN
Challenges in the ICU

- Multidisciplinary teamwork
- Continuity of 24/7 care
- Rapidly transforming environment
- Translation and implementation of evidence from research
- Individualisation of treatment
change our research paradigm to implement evidence into our daily practice
change our research paradigm to truly individualise treatment
Large randomised clinical trials in ICU

They are always negative!
Benefit or harm subgroups may go undetected
• 72 RCTs identified, assessing effect on mortality
  • 55 no effect
  • 7 detrimental effect
  • 10 beneficial effect

Interventions from the positive trials not implemented in real life
Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries

Giacomo Bellani, MD, PhD; John G. Laffey, MD, MA; Th Pham, MD; Eddy Fan, MD, PhD; Laurent Brochard, MD, HDR; Andres Esteban, MD, PhD; Luciano Gattinoni, MD, FRCP; Frank van Haren, MD, PhD; Anders Larsson, MD, PhD; Daniel F. McAuley, MD, PhD; Marco Ranieri, MD; Gordon Rubenfeld, MD, MSc; B. Taylor Thompson, MD, PhD; Hermann Wigge, MD, PhD; Arthur S. Slutsky, MD, MASC; Antonio Pesenti, MD, for the LUNG SAFE Investigators and the ESICM Trials Group

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The diagram shows a scatter plot with the x-axis representing Tidal Volume (mL/kg of Predicted Body Weight) ranging from 1 to 15, and the y-axis representing Plateau Pressure (cm H₂O) ranging from 10 to 40. The plot is divided into categories of mild, moderate, and severe ARDS, with different colors representing these categories.

- Mild (n=5): 40% of the points are scattered in this region.
- Moderate (n=21): 25% of the points are scattered in this region.
- Severe (n=30): 35% of the points are scattered in this region.

On the right side of the plot, the categories are:
- Mild (n=2): 2% of the points are scattered in this region.
- Moderate (n=8): 5% of the points are scattered in this region.
- Severe (n=12): 7% of the points are scattered in this region.

The overall percentage of patients with severe ARDS is indicated by the text "64%" at the bottom of the plot.
What good are trials if the results aren’t applicable to real-world patients and if, because of excessive expense, they can be used to answer only a tiny fraction of our important clinical questions?
One possible solution is to look to observational registries for answers.
Observational (Big) Data
When do confounding by indication and inadequate risk adjustment bias critical care studies? A simulation study
does this treatment work?
randomization is mandatory
Conventional trial

1:1 randomization

Adaptive trial

If a subgroup starts doing better with one treatment, randomize more to that treatment
Example traditional RCT
Example traditional RCT
Severe Community Acquired Pneumonia

Scenario: **steroids** are beneficial for the subgroup with **shock**
more patients with shock to steroids

looks like patients with shock are doing better with steroids

data

conduct an interim analysis
data

conduct an interim analysis

randomize more patients with shock to steroids

still looks like patients with shock are doing better with steroids
randomize more patients with shock to steroids

99% chance that steroids are better than no steroids if you have shock

all patients with shock now get steroids

conduct an interim analysis

data
patients without shock continue to be randomized to steroids vs. placebo

≥90% chance that steroids are not better than no steroids if you have do not have shock

conduct an interim analysis

study arm ceases
# The Platform Trial
An Efficient Strategy for Evaluating Multiple Treatments

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Traditional Trial</th>
<th>Platform Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scope</td>
<td>Efficacy of a single agent in a homogeneous population</td>
<td>Evaluating efficacy of multiple agents in a heterogeneous population; explicitly assumes treatment effects may be heterogeneous</td>
</tr>
<tr>
<td>Duration</td>
<td>Finite, based on time required to answer the single primary question</td>
<td>Potentially long-term, as long as there are suitable treatments requiring evaluation</td>
</tr>
<tr>
<td>No. of treatment groups</td>
<td>Prespecified and generally limited</td>
<td>Multiple treatment groups: the number of treatment groups and the specific treatments may change over time</td>
</tr>
<tr>
<td>Stopping rules</td>
<td>The entire trial may be stopped early for success or futility or harm, based on the apparent efficacy of the single experimental treatment</td>
<td>Individual treatment groups may be removed from the trial, based on demonstrated efficacy or futility or harm, but the trial continues, perhaps with the addition of new experimental treatment(s)</td>
</tr>
<tr>
<td>Allocation strategy</td>
<td>Fixed randomization</td>
<td>Response-adaptive randomization</td>
</tr>
<tr>
<td>Sponsor support</td>
<td>Supported by a single federal or industrial sponsor</td>
<td>The trial infrastructure may be supported by multiple federal or industrial sponsors or a combination</td>
</tr>
</tbody>
</table>
A Bayesian response-adaptive trial in tuberculosis: The endTB trial.

Cellamare M¹, Ventz S², Baudin E³, Mitnick CD⁴, Trippa L⁵. 2016 Aug 23

- Evaluation Bayesian adaptive randomisation for clinical trials
- MDR TB, 5 experimental regimens, 1 control arm
- Response-adaptive randomisation, 2 preliminary outcomes
- Primary outcome: treatment success after 73 weeks
- Several hypothetical scenarios
A Bayesian response-adaptive trial in tuberculosis: The endTB trial.
Cellamare M, Ventz S, Baudin E, Mitnick CD, Trippa L. 2016 Aug 23

• Results, adaptive design versus non-adaptive:
  • Allocation: consistently more patients allocated to effective arm(s)
  • Power: fewer patients required
I-SPY 2 — Toward More Rapid Progress in Breast Cancer Treatment

Lisa A. Carey, M.D., and Eric P. Winer, M.D.
A Bayesian comparative effectiveness trial in action: developing a platform for multisite study adaptive randomization.
Adaptive Design platform for Severe Community Acquired Pneumonia (AD-SCAP)

- Drug: Antibiotic A
- Drug: Antibiotic B
- Drug: Hydrocortisone

3 treatment domains

- Device: Minimal distension
- Device: Maximal recruitment
- Device: ECCO2R

12 study arms
adaptive platform

trials

fusion of trial science

and continuous quality improvement
saves lives by incorporating treatments that save lives into standard care
save money by not using treatments which are ineffective
change practice in ICU
implement evidence
individualise treatment