

# New, Flexible Approach to Drug Development

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**Chair, Athenaeum Group**

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# THE PROBLEM – for patients, researchers and industry

- **The current drug development model is unaffordable**
  - R&D costs increase, no. of first launches decrease, so productivity is poor
  - EU CT Directive has added to increased complexity and data demands
- **Current model is too inflexible in process, timing and methods**
  - Progressive escalation in complexity, cost and time
  - One model does not fit all
  - Pricing and reimbursement processes are additive barriers or deter R&D
- **Lack of alignment and partnership between stakeholders- and innovators**
  - Competitive & adversarial attitudes can be counterproductive- balance needed
  - Discussion & decision making in sequential silos
  - Access issues are addressed separately and after most of the R&D invested
- **Patients need innovative therapies more rapidly**
  - Feel disconnected from the process meant to be for their benefit
  - Benefit/risk assessments made by others (innovators and regulators)

# ATHENAEUM GROUP

- A forum to:
  - Share ideas, develop solutions, publicise them and drive them forward
  - Integrate disparate changes in a new model
  - Syndicate with others (across organisational boundaries and globally)
  - Initiate or catalyse action
  - Encourage pilots to test and refine the ideas
  - Overall, to ensure that the solutions meet the core needs of patients – i.e. to have rapid access to essential new medicines with acceptable benefit/risk balance

# ATHENAEUM GROUP

## multi-stakeholder

- Chair - Richard Barker, ABPI
- Regulatory : Thomas Lonngren, Hans-Georg Eichler (EMA)  
Alasdair Breckenridge (MHRA); Gordon Duff (CHM)
- Industry : Jeremy Haigh (Amgen); Anton Hoos (GSK) ; Jeremy Knowles, Philippe Van der Auwera (Roche); Hilary Malone, Robin Evers (Wyeth); Beatrix Friedeberg (AZ)
- Government : David Cooksey
- HTA : Michael Rawlins, Carole Longson ( NICE)
- Academia : John Bell (Acad Med Sci, OSCHR); Adrian Towse (OHE); Stuart Walker (CMR)
- Patients - Mary Baker (EU FNA)
- Industry expert: Frances Macdonald

*Note: This presentation is for discussion and does not represent the policy of any of the organisations listed*

# LOTS OF 'STRAWS IN THE WIND'

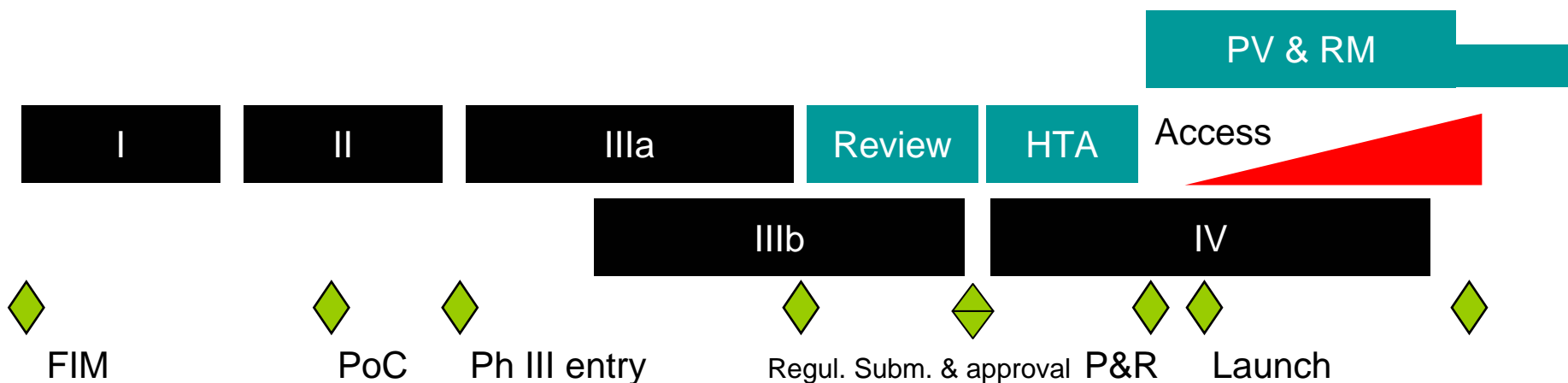
Governments:

- Critical Path Initiative (FDA)
- Innovative Medicine Initiative (EU)
- Cooksey Report (2006)

Plus:

- Professor Rawlins' 2008 Harverian Oration on research methods
- Sensible approaches for reducing clinical trial costs  
Eric L Eisenstein et al, Clin Trials; 2008; 5; 75
- Harmful Impact of EU clinical Trial Directive:  
A Hemminki and P-L Kellokumpu-Lehtinen. BMJ 2006;332;501-502
- A Bayesian approach to trials:  
M L Lee and D A Roth, Haemophilia (2005), 11, 5-12  
D Berry ; Nature Reviews/Drug Discovery ; 2006; 5 ;27-36
- The Economics of Personalized Medicine: A Model of Incentives for Value Creation and Capture  
L Garrison and M Austin; Drug Information Journal,2007; 41, pp. 501 – 509,

# Current development path



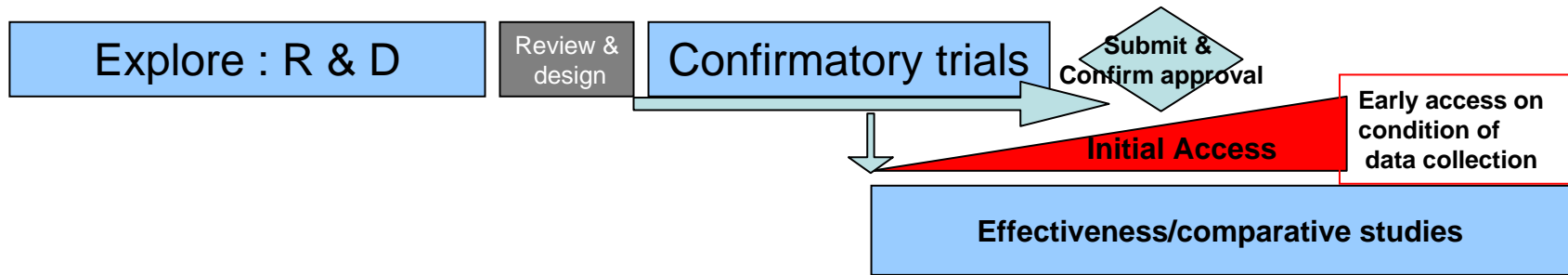
## Key characteristics of current model

- **Inflexible** processes and methods
  - **Expensive**, increasing data demands
- **Lack of early alignment** between key parties:
  - Segmented input & decision making
- **Access** Needs- not designed in
- Patient perspective - not fully addressed

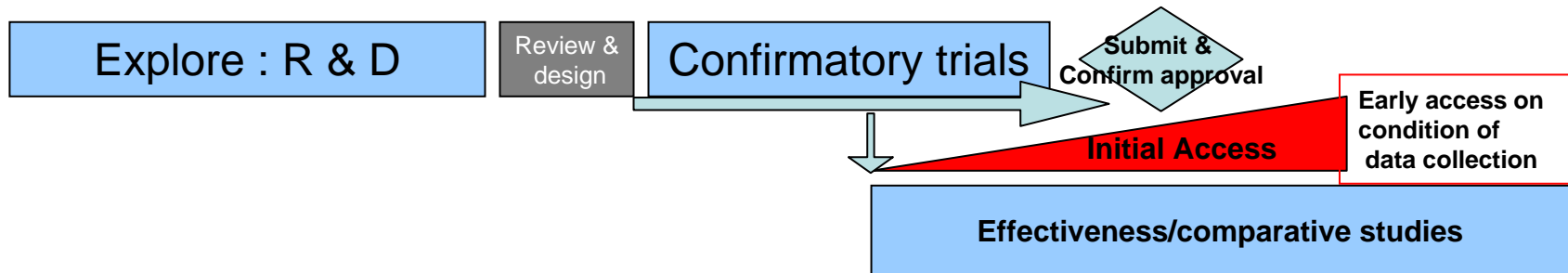
External activities

Sponsor activities

# Potential new flexible blueprint



# Potential new flexible blueprint



## Key Features:

- Basic division between exploratory and confirmatory trials rather than Phases I-IV
- Collaborative design step before the most expensive confirmatory trials are commissioned
- Ability/need to customise the model for different benefit/risk/uncertainty profiles
- Ability to allow early, controlled patient access if justified by interim findings of confirmatory trials
- But subject to requirements for pharmacovigilance and pharmacoeconomic analysis before full 'green light' for wide access and longer term reimbursement policy

# Seven Priority Areas for Action

## – for clinical researchers and others (1)

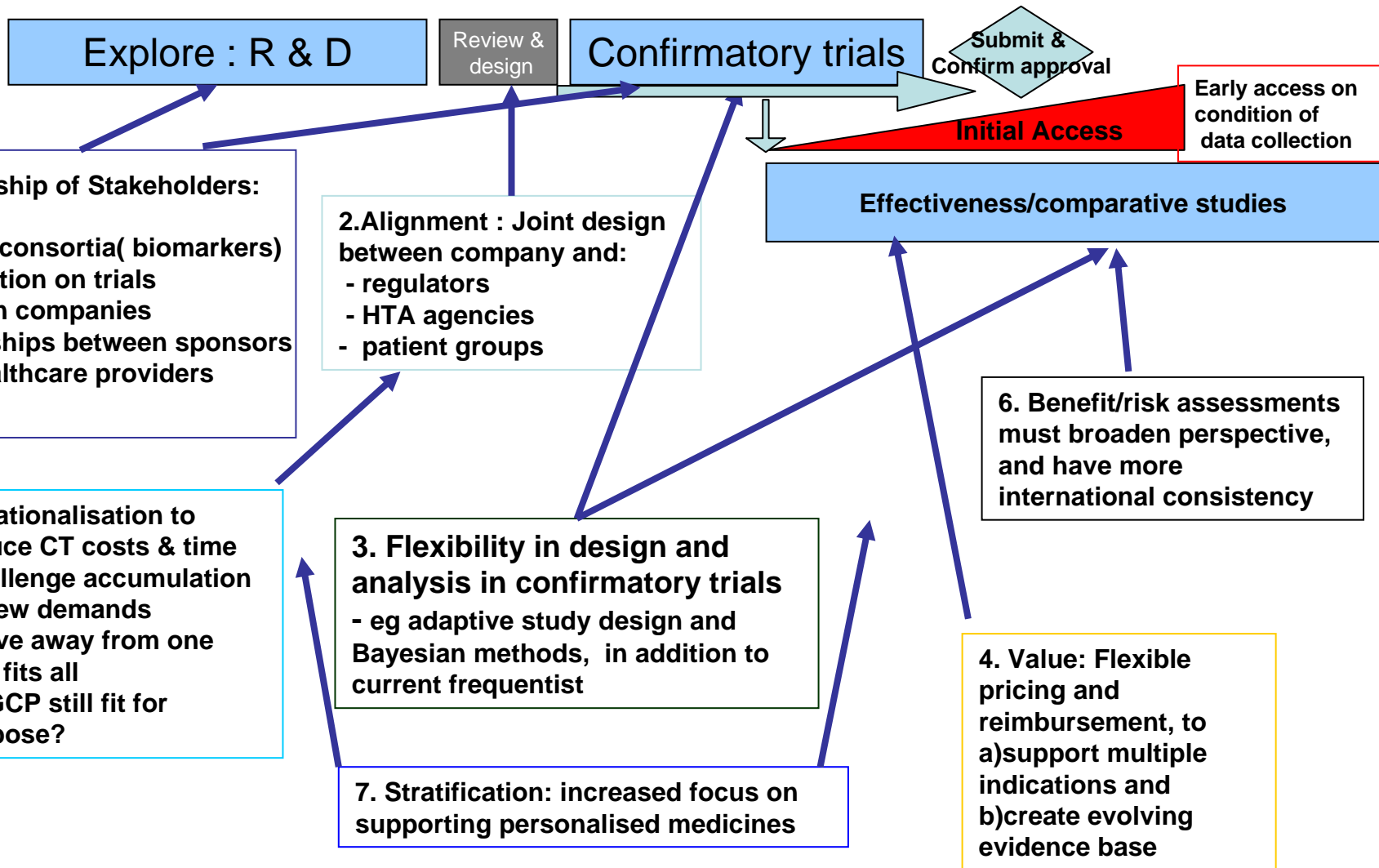
- 1. Partnership** - Increased pre-competitive collaboration between innovators, plus broader stakeholder partnerships (eg via disease area partnerships) in order to share expertise, risk and cost
- 2. Alignment** – mid-development agreement on alignment of innovator, regulator and reimbursement needs from trials
  - At this point largely a European issue
  - Some progress at national level; eg UK, Sweden, Canada
- 3. Flexibility** - in *timing* of trials, and in the range of accepted *methodologies for design and analysis* of confirmatory trials
  - Frequentist methods are not always the most suitable
  - Comparative efficacy studies are increasingly called for

# Seven Priority Areas for Action

## – for clinical researchers and others (2)

4. **Value** elements to support pricing and reimbursement:
  - Collect 'value' data for payers alongside efficacy/safety data
  - Allow flexibility in evaluation processes in order to reduce termination of potentially valuable indications and support multiple indications
5. **Rationalisation** of the component elements of R&D and thus reduce costs.
  - Impact of EU CT Directive needs addressing
  - More international alignment of data requirements and logistics
  - Simplified data/audit needs based on specific risk not all conceivable risk
6. **Benefit/Risk** assessment
  - Must be more systematic, transparent and take a broader perspective, incl. patients
  - Significant difference between regional decisions (eg EMEA & FDA) must be addressed
7. **Stratification** – making 'personalised medicine practical - finding and standardising biomarkers, aligning the regulators, dealing with reimbursement issues.

# Potential new flexible blueprint



# Customisation is critical ...

- (a) **Novel medicines in areas of high unmet medical need**, where few or no alternatives exist. Here adaptive trial design and the collection of robust HTA-ready data, in the course of confirmatory trials, could reduce time-to-patient and the risk of reimbursement refusal.
- (b) **Medicines exploiting new mechanisms of action in an indication in which there are already well-established therapies**. Here the design of the late stage 'effectiveness studies', involving active comparators, will be key to gaining reimbursement.
- (c) **A new indication for an existing approved medicine**, in which an adaptive trial design can incorporate safety data already gathered in previous studies, and variable pricing and reimbursement arrangements will be key.
- (d) **Novel medicines for major areas of unmet chronic disease** need, such as Alzheimers, where trial consortia, partnering between health systems and innovators and adaptive trial design may all be necessary to make the trials affordable.

# Issue 5 – Rationalisation.

## Example: Clinical Trial Directive (2004)

### Objectives

- Harmonised procedures ( Competent authorities / Ethics Committees)
- Protection of human subjects in clinical research
- Implementation of GCP in all trials
- Central collection of information on CT activities and safety results

### 5 years on.... (1)

- Regulatory approval timelines reduced across EU as a whole
- Quality requirements harmonised **but...**
- Safety data reporting handled differently across EU
- Increased administrative burden, esp. for non-commercial sector
- Increase in time from protocol finalisation to first-patient-in
- Decreased CT activity in non-commercial sector (- 25%) across EU
- Some increase in CT activity for commercial sector (+11%)

1) *Impact on Clinical Research of EU Legislation (ICREL) Project Report, Dec 2008, [www.efgcp.be](http://www.efgcp.be) /ICREL*

**This raises concerns for Europe's attractiveness in clinical research !**

# Competent Authorities

- Average CTA timelines 49 days (well within stipulated max. 60 days)
- Rise in fees
- Substantial amendments and SUSAR reports increased
- Difference in definitions across EU (e.g. 'investigational medicinal product', Sponsor, Substantial Amendments) <sup>(2)</sup>

# Ethics Committees

- CT Directive requires one single EC opinion but still involves several ECs in many countries
- Increased workload for ECs
- Annual budget increased on average by 50%
- Higher numbers of substantial amendments / SUSARs
- 60% of ECs without patient representation

2) EFGCP report: A Single CTA in Multinational Clinical Trials – Dream or Option, July 2009

# Non-Commercial Trials, UK

- Increased approval times
- Increased costs (including insurance)
- Strengthened responsibilities for sponsors make it difficult to find sponsors for non-commercial trials
- Directive places same requirements on trials with new and marketed drugs, leading to obstacles for academic research

# What Europe needs to retain clinical research (2)

- Simplified and truly harmonised requirements across Europe
- Reduced administrative burden and faster overall implementation of CTs
- A review of current legislation – *now anticipated for early 2010*
- Proportionate approach to safety reporting
- Ethics review in parallel to Authority review
- Clarification of roles and responsibilities of research EC
- Support for CT insurance / infrastructure for academic trials
- End of confusion of key terminology / definitions
- Training for academia, ethics (and regulators)
- **Harmonised review of CT ('Centralised Approval')**
  - NB: 60% of all CTs in the UK are carried out in more than one MS (3)
- **Rationalisation of other parts of 'red tape' to make Europe more efficient in R&D**
- **Make best use of national databases**

2) EFGCP report: A Single CTA in Multinational Clinical Trials – Dream or Option, July 2009

3) Disharmony Stifling Research in Europe, Applied Clinical Trials, August 2009

# SOME POSSIBLE QUESTIONS FOR DISCUSSION

- Is this new, flexible model a step forward?
- What changes might we be missing? E.g. Tort reform?
- Which are the most important impact areas, from the cost and time standpoint? E.g. SAE reporting?
- How can public/academic and private sector players cooperate in bringing change about? Beyond forums like this ...
- Are we taking a sufficiently proportionate and innovative approach ?
- How can we work better cross-regionally to improve efficiency globally ?

# CONCLUSIONS

- The problem is now urgent – patients can't wait, industry productivity must improve, trials and medicines must be affordable
- We need a new, flexible model accepted/welcomed by all stakeholders
- There are several areas of advance to be integrated into the model
- We need investigators and companies ready to pilot the changes