Safeguarding public health

Regulatory Agencies and Quality in Clinical Trials
Risk Adaptive Approach

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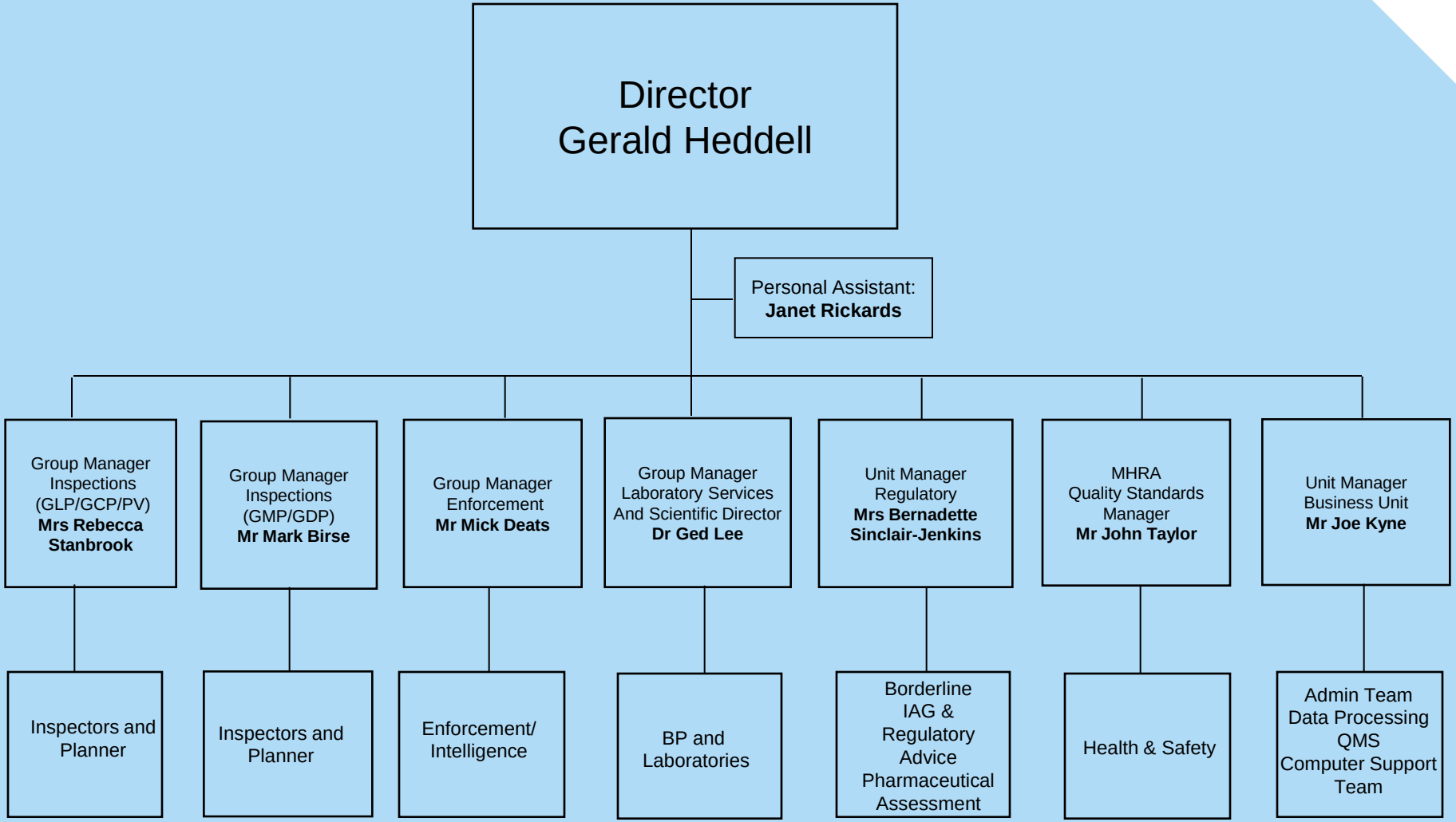
August 2011

MHRA

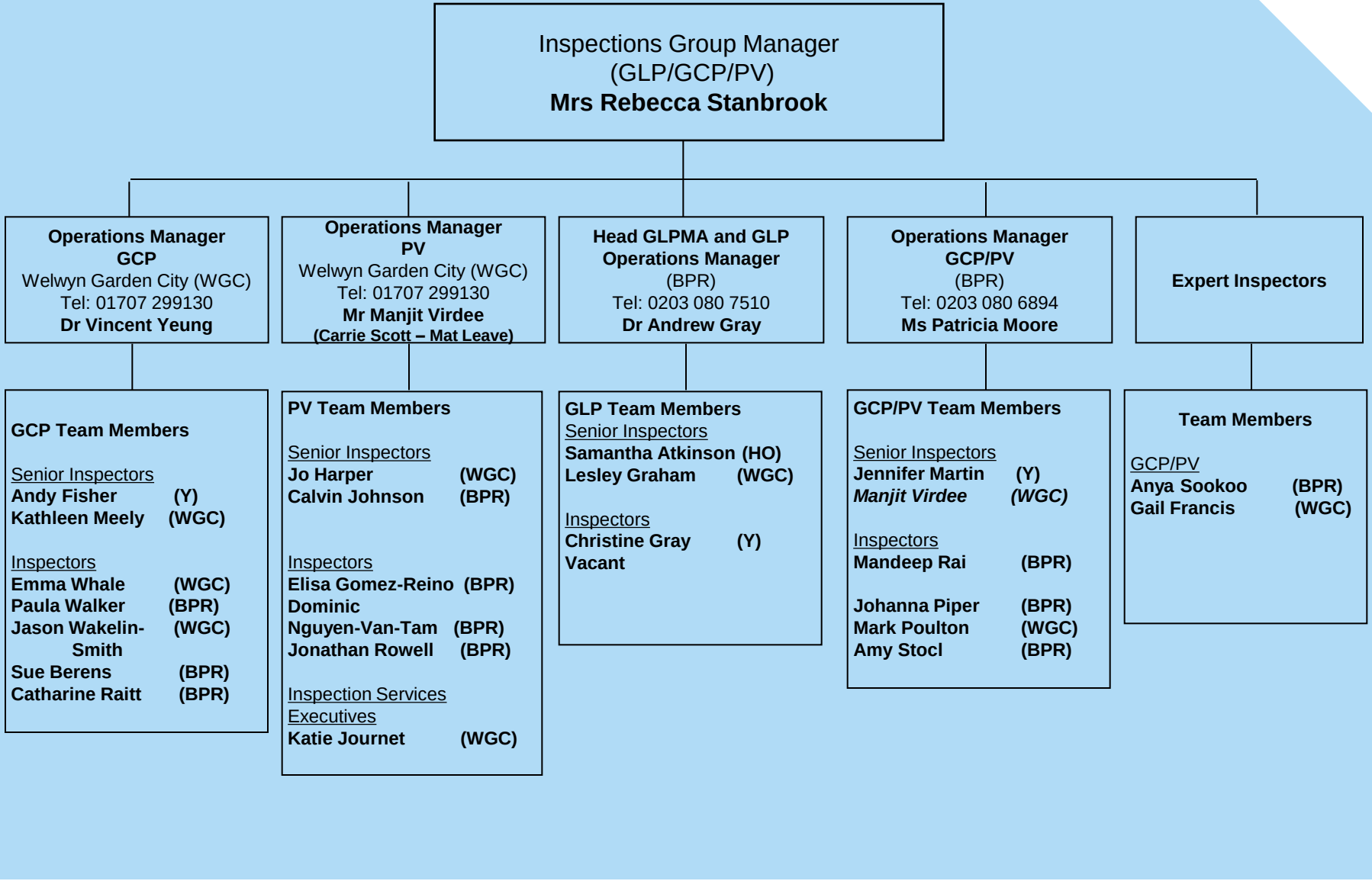
Aims of the Agency

- Protecting public health through regulation, with acceptable benefit-risk profiles for medicines and devices.
- Promoting public health by helping people who use these products to understand their risks and benefits.
- Improving public health by encouraging and facilitating developments in products that will benefit people.

Inspection, Enforcement & Standards Division



Inspection, Enforcement & Standards Division



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Risk Adaption – what is it?

- OECD – Global Science Forum
  - Risk based approaches
    - Stratified
    - Customised

- EMA
  - Reflection paper
    - Risk based Quality management in clinical trials

- UK
  - AMS report
  - Growth Agenda
  - DH/MRC/MHRA project

MRC/MHRA/DoH Project Scope

- Focus on ***risks inherent in the protocol*** for
    - Participant safety to the trial intervention
      due to the trial intervention & clinical procedures
    - Participant rights
      due to inadequacy of the consent process & failure to protect participant data
    - Reliability of results
- Implementing a risk based Quality System

⇨Informed protocol development
⇨Targeted management and monitoring plan

Approach

- Work within current legislation/guidance
- Identify what can be done differently/less of for certain types of trial?
  - Application process
  - Conduct of the trial
- Implement and develop guidance

Risk based approach for assessment

- Type A trials - CTA notification only to MHRA
  - Default approval after 14 days
  - Limited triage/assessment internally
  - Potential to object to Notification – full assessment
  - Amendments
    - Not substantial if within SmPC (Type A) – no submission needed
    - Submission for substantial – beyond SmPC
- Live from 1st April 2011

1. Intervention Safety Risk

- Assess risk associated with trial interventions (IMP)
- Assess risk in relation to normal standard care
    - Comparable to standard care **(Type A)**
    - Somewhat higher than standard care **(Type B)**
    - Markedly higher than standard care **(Type C)**

Intervention Safety Risk – Type A

Trial Categories based upon the potential risk associated with the IMP	Examples of types of clinical trials
Type A: no higher than **that of standard medical care**	**Trials involving medicinal products licensed in any EU Member State if:** **▪they relate to the licensed range of indications, dosage and form** **or, they involve off-label use (such as in paediatrics and in oncology etc) if this off-label use is established practice and supported by sufficient published evidence and/or guidelines**

Intervention Safety Risk – Type B

Trial Categories based upon the potential risk associated with the IMP	Examples of types of clinical trials
Type B: somewhat higher than that of standard medical care	Trials involving medicinal products licensed in any EU Member State if: ▪such products are used for a new indication (different patient population/disease group) or ▪substantial dosage modifications are made for the licensed indication or ▪if they are used in combinations for which interactions are suspected Trials involving medicinal products not licensed in any EU Member State if ▪the active substance is part of a medicinal product licensed in the EU (A grading of TYPE A may be justified if there is extensive clinical experience with the product and no reason to suspect a different safety profile in the trial population)*

Intervention Safety Risk – Type C

Trial Categories based upon the potential risk associated with the IMP	Examples of types of clinical trials
Type C: markedly higher **than that of standard medical care**	**Trials involving a medicinal product not licensed in any EU Member State** **(A grading other than TYPE C may be justified if there is extensive class data or pre-clinical and clinical evidence)***

2. Non IMP risks

- Risks related to the design and methods of the trial
  - participant safety and rights
  - reliability of results

- Multi-factorial and less amenable to simple categorisation at the trial level.
- Must be assessed independently and mitigation plan developed

  - *Identify areas of vulnerability*
  - *Specify mitigation and management plan*
  - *Can trial monitoring detect/reduce potential for error?*

⇨Targeted management and monitoring plan
⇨Informed protocol development

Impact on Authorisation

- Type A trials - CTA notification only to MHRA
  - Default approval after 14 days
  - Limited triage/assessment internally
  - Potential to object to Notification – full assessment
  - Amendments
    - Not substantial if within SmPC (Type A) – no submission needed
    - Submission for substantial – beyond SmPC

Risk Adaption in Practice

- 11 trials have gone through the Risk Adaptive Process since April 2011

Implementation & Plans

- Risk Adaptation implemented 1st April 2011
- Appendix 2 (Guidance for risk assessment etc) has been piloted by a group of CTUs
- Appendix 2 to be reviewed and issued (anticipate September)
- The GCP inspectorate will produce guidance on areas where risk adaptation would be appropriate.
  - First guidance will be on monitoring
- Consultation on guidance and examples
- Web to contain guidance and populate with examples (provided via inspection, volunteered or forum)
- Development and planned publication of GCP Guide

Risk Adaptation Areas

IMP

Monitoring & Sponsor Oversight

CT Pharmacovigilance

Training

Laboratories

Quality Systems & QA

Data Management

Statistics

Reporting

Computer Systems

Trial Master Files & Archiving

Risk Adaptations	Areas impacted
1. Reduced MHRA role in approvals	Notification v Approval
2. Content of application	a) IMP dossier b) Investigator's Brochure c) GMP Compliance
3. Labelling of trial drugs	a) Need for trial labelling b) Content of labelling
4. Safety Surveillance	a) Adverse Drug Event recording/reporting b) Safety Monitoring
5. IMP management	a) Tracking and Accountability b) Storage
6. Documentation	a) TMF Content b) Essential Documents retention times
7. GCP Inspections	a) Organisation and selection processes for routine GCP systems inspection b) Increase in routine GCP inspection reviews at the study level c) Frequency and duration of inspections

Thank you for your attention

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