THE PRINCIPLES OF CLINICAL SUPPLY
- And How to Improve Efficiency and Cost Effectiveness

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Principal IRT Manager, LEO Pharma A/S
AGENDA

OVERVIEW

- CTS Activities
- IRT Systems
- EU CTR (536/2014)

TRENDS / GUIDANCE

- Patient Kit Design
- Supply Chain Optimization
- Limited Drug
CLINICAL SUPPLY CHAIN

LET’S START WITH THE BASIC PRINCIPLES
PACKAGING AND LABELLING
Clinical labels, Translations, Blinding, Kitting

STORAGE
Warehouse management, Regional Depots

CLINICAL SITE
Drug Handling Guidance, Storage

PRODUCTION
Clinical Forecasting, Comparator and Ancillary Sourcing

DISTRIBUTION
Controlled shipment, supply plans, Import/Export, IRT

RANDOMIZATION AND DRUG DISPENSING
IRT, Patient Direct Shipment

RECONCILIATION AND RETURNS
Drug Compliance, Archiving
SOME CONSIDERATIONS

PACKAGING AND LABELING

Be careful for varied retest dates
- Potential un-blinding if only replacing kits for a single arm

Avoid single panel labels (if possible)
- Ensure the greatest flexibility

Use color and pictograms
- Will enhance site and patient compliance in dosing

Avoid to pack scheduled drug in the same dispensing kit as unscheduled
- Limited space at site

Use labels suitable for the intended temperature range and use
- Freeze / Thaw; Twisting bottle etc.

Leave room on the labels for additional label (if possible)
- Useful when changing use-by-date
STORAGE AND DISTRIBUTION - GDP

STOCK TRANSFERS  QUALITY AGREEMENTS  INVENTORY MANAGEMENT  TEMP LOGGERS  IRT  SITE STORAGE

IMPORT/EXPORT  INSURANCE  TEMP. DEVIATIONS  SHIPPERS  CUSTOMS  EXPIRATION TRACKING  COLD CHAIN
ENSURE THAT APPROVALS ARE IN PLACE
• QP Cert.
• Submission of paperwork to custom
• Regulatory Green Light (EC and approved submission)

ENSURE THAT TEAM IS READY
• QA is informed, to quickly resolve any temperature deviation
• Local CRA is informed etc.

ENSURE KITS ARE “SHIPPED” IN IRT
• In order for the site to acknowledge drug receipt

ASK FOR THE AWB NUMBER
• Track and Trace
• Check that the AWB number is uploaded in systems
• Review/Check completed shipment documents (incl. invoices, certificate etc.)

ENSURE THAT TEAM IS READY
• QA is informed, to quickly resolve any temperature deviation
• Local CRA is informed etc.
INVESTIGATIONAL SITE AND PATIENTS - GCP
THE CLINICAL SUPPLY MANAGER / TEAM

WORKS WITH MULTIPLE-DISCIPLINES

CLINICAL TRIAL MANAGER / CRAs
Incl. Field monitors and site coordinators

CMC and R&D PROJECT MANAGER
Incl. Toxicologist (Phase 1 trials) and stability scientist

QA and Regulatory
Incl. Qualified person, QA auditors

DATA MANAGER AND BIOSTAT
Incl. statistical programmer

IRT VENDOR
Incl. CTMS administrators, forecasting analyst etc.

PACKAGING CMO AND CLINICAL CRO
Incl. third party depots, courier companies and various service providers
EU CLINICAL TRIAL REGULATION
IMPLICATION FOR CLINICAL SUPPLIES MANAGEMENT
FROM DIRECTIVE TO REGULATION

2001/20/EC

COMES INTO FORCE

EU PORTAL GO-LIVE

SINGLE PORTAL

CTR EU No. 536/2014 (PUBLISHED IN MAY 2014)

NEW EU CLINICAL TRIAL REGULATIVE

PHASED OUT

2001/20/EC NO LONGER APPLICABLE

MAY 2004
SEP 2018
OCTOBER 2018
OCTOBER 2021
What is coming with regards to CTR EU No. 536/2014

- Centralized / Single Application Process – EU Portal
- AMP will replace NIMP
- Reporting of Trial Progress
- Harmonized Conduct of Trials
- Simple Reporting of SUSARs
- Co-Sponsorship
- Clinical Data Transparency (EU Database)
- Binding for all Member States
- Clinical Data Transparency
- Co-Sponsorship
“AMP” Replaces “NIMP”

DEFINTION
“AMPs are related to the design of a clinical trial, but are not considered as Investigational Medicinal Product (IMP), e.g. background medication, rescue medication, diagnostics etc.”

• PROVIDE RATIONALE FOR USE OF AMP IN PROTOCOL

AND

• AUTHORIZATION STATUS
Labeling Requirements for IMP/AMP (Chapter X and ANNEX 6)

- STANDARDIZED LABEL CONTENT
- NO ADDITIONAL LABEL TO AUTHORIZED AMP COMMERCIAL LABEL NEEDED
- LABELING OF UNAUTHORIZED AMPs ARE ALMOST IDENTICAL TO UNAUTHORIZED IMPs
Re-test or Expiry date Labeling of IMP/AMP (ANNEX 6)

- Expiry date / Re-test on all inner containers (immediate / primary pack)
- Without exception! (NO IRT…)

OBS. When updating Expiry / re-test date
PATIENT KIT DESIGN

PATIENT COMPLIANCE AND PERCEPTION
PACKAGING AND LABELING CONSIDERATIONS

- Keep the IMP flexible
- Expiration date of all products being packaged together.
- Space at site
- No kits are pre-assigned to subjects
- If possible, keep the different types separate.
- Minimize the packaging materials.
THE FOCUS IS CHANGING AND WE NEED TO TRY AND BALANCE THIS...

BEFORE

TRADITIONALLY
UPSTREAM ACTIVITIES

COMPLIANCE WITH cGMP
and cGDP

NEW SCHOOL
PATIENT CENTRICITY

PATIENT ADHERENCE
AND PROTOCOL
COMPLIANCE
Patient Experiences with Clinical Trial Materials

The Role of Medicine Kit Design and Labeling in Patient Compliance

Patients involved in this project reported that clarity of instructions and ease of use are the two most important medicine kit factors from their perspectives.

Most Important Medicine Kit Factors

- Clarity of instructions: 69%
- Ease of use: 64%
- Information on the label: 47%
- Ease of storage: 45%
- Size and weight: 36%
- Single doses inside the medicine kit: 36%

*Base: All respondents n = 1,425  No significant differences among age and therapeutic areas.*

With this in mind, the project data shows that medicine kit design and labeling could play an even stronger role in assisting compliance.

- Kit design and labelling could assist compliance through clear information
- Commit to clear instruction for both patients and sites
INTRODUCTION TO OPTIMIZATION OF CLINICAL SUPPLY
And Strategies for Limited Drug Availability
WHY IS OPTIMIZING SO IMPORTANT?

TRIALS ARE INCREASINGLY BECOMING MORE COMPLEX
With more countries and sites in emerging regions - regulatory challenges.

BIOLOGIC DRUGS / COSTLY SUPPLY
More expensive drug product that requires Cold Chain Management

MORE AND MORE TRIAL ARE USING COMPARATORS
That may have to be bought on the commercial market to retail prices

AS A RESULT, AN INCREASED COST!
OPTIMIZATION IS MORE THAN JUST REDUCING COST

THESE ARE THE BUILDING BLOCKS

QUALITY
DELIVER DRUG IN THE RIGHT QUALITY

SPEED
INCREASE SPEED IN WHICH SUPPLY CAN BE MADE AVAILABLE

FLEXIBILITY
INCREASE FLEXIBILITY OF SUPPLIES

COST
REDUCE COST
WHAT ARE WE TRYING TO ACHIEVE?

REDUCE TIMELINES AND COST AT THE SAME TIME WITHOUT AVOID DISRUPTION OF DRUG TO PATIENT

ENSURE THAT THERE IS ENOUGH DRUG AT SITE BUT NOT TOO MUCH TO AVOID WASTE AND SHORTAGE AT OTHER SITES
IMPLEMENT SUPPLY OPTIMIZATION THROUGHOUT THE PROCESS

FROM THE EARLY
1. PROTOCOL DEVELOPMENT

AND DURING THE
2. PLANNING PHASE

AND THROUGHOUT THE
3. TRIAL CONDUCT / EXECUTION
TO GET THE RIGHT DRUG TO THE RIGHT PATIENT IN RIGHT TIME IN THE RIGHT CONDITION... YOU SHOULD CONSIDER:

**STUDY DESIGN**
Titration, weight, visit windows, randomization scheme

**EXPIRATION AND RETEST DATES**
Resupply packaging lead-times

**SHIPPING LEADTIMES**
From depot to depot and depot to site and from site to patient home

**ENROLLMENT RATES AND DYNAMICS**
And change in site status can affect supply plans.

**STORAGE SPACE AT SITE**
And the size of the shipper

**CUSTOMER SERVICE**
Maintain good relationship with investigator (and trial manager)
A close communication and relationship with the clinical team is important.

"Loads of data can be "mined" from eclinical systems so use that information to start drive decision making."

...and communicate the metrics (KPIs) !!!
SOME VALUABLE METRICS THAT REVEALS POTENTIAL PROBLEMS DURING THE STUDY

**FORECAST ACCURACY**
- Study initiation date
- Dropout rate
- Registration of visits in real-time

**DISTRIBUTION**
- One time delivery: Actual vs expected
- Number of expedited shipments
- Number of countries and sites

**QUALITY**
- Temperature deviations / excursion (normalized for volume)
- Time to close deviations
THE BENEFITS OF AN OPTIMIZED SUPPLY CHAIN

<table>
<thead>
<tr>
<th>Reduced Inventory and Storage Cost</th>
<th>Less Return Shipments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shortened Study Timelines</td>
<td>Minimal Drug Wastage</td>
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<tr>
<td></td>
<td>Reduced Reconciliation</td>
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STRATEGIES FOR WHEN DRUG IS LIMITED
### USEFUL STRATEGIES WHEN THE DRUG SUPPLY IS LIMITED AND OR COSTLY

<table>
<thead>
<tr>
<th>IRT SYSTEM</th>
<th>“Clever” Supply Plans</th>
<th>Simulate / Forecast Supply Needs</th>
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<tbody>
<tr>
<td>Avoid to ship out in blocks – Central randomisation</td>
<td>Ship only to sites when there is patients – no frontloading and only the kits associated with patient’s treatment group</td>
<td>Will help you optimize production and distribution strategies</td>
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<td>Product pooling – any kit may go to any patient</td>
<td></td>
<td>Integrate with IRT for realtime updates</td>
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<td>Predictive resupply – look ahead on rand list</td>
<td></td>
<td>Analyze supply impact due to change in enrollment</td>
</tr>
<tr>
<td>Realtime patient and drug supply tracking</td>
<td></td>
<td>Test of “what-if” situations e.g adaptive study designs</td>
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USE TECHNOLOGY SOLUTIONS

STREAMLINE QA PROCESSES

MONITOR SUPPLIES

KEEP THE SUPPLY FLEXIBLE

AVOID TO SHIP IN “BLOCKS”

IMPLEMENT CREATIVE SUPPLY STRATEGIES
IRT

When, How and the interplay with other e-clinical systems
ADVANTAGES OF IRT

PRODUCT POOLING

DRUG NOT LINKED TO PATIENT BEFORE DISPENSATION

INVENTORY MANAGEMENT

END-TO-END DRUG ACCOUNTABILITY

CONTROLLED RANDOMIZATION

BALANCED

VISIBILITY

KNOW WHEN DRUG ARE ASSIGNED TO PATIENT
THE IRT LIFECYCLE

1. DESIGN / BUILD
2. INTEGRATE
3. TEST / IMPLEMENT
4. MAINTAIN / SUPPORT
5. CLOSURE

URS / CONFIGURATION REPORT

DATA INTEGRATION AND TRANSFER NEEDS

REPORTING AND DATA EXTRACTS (E.G. ALLOCATION DATA)

MONITOR AND ADJUST

UAT

IRT

REPORTING AND DATA EXTRACTS (E.G. ALLOCATION DATA)

UAT
SELECTING AN IRT SYSTEM

GOLDEN RULES
(or wish-list)
POTENTIAL

PITFALLS TO AVOID

- “OVER-DESIGNING” THE SYSTEM
- SELECTING A 100% “NON-CONFIGURABLE” SYSTEM
- IMPLEMENTING “HARD-STOPS”
- DEVELOP BEFORE ”FINAL” STUDY DESIGN
- ONLY PROVIDING TRAINING OF SITE STAFF – REMEMBER THE DEPOT
- RELY ON “DEFAULT” SETTINGS
- SHARE KNOWLEDGE OF RANDOMIZATION ALGORITHM – UNBLINDING!
INTEGRATED SOLUTION – MANY… MANY SYSTEMS IN THE FUTURE

NOT ONLY ONE LOGIN WITH ACCESS TO ALL SYSTEM BUT ABILITY TO CREATE ACTION !!!
FUTURE TREND WITHIN CTS?

Business Analytics And Data Visualizations Tools

… Take more informed operational decisions in real-time using hundreds streams of data and discover patterns.

… And make more sense of clinical data when shared!
REFERENCES


