THE EXPERIENCE OF CRO BASED IN RUSSIA
Clinical Trials in Russia and Ukraine: Regulatory, Operational and Clinical Aspects

PREMIER RESEARCH RUSSIA: MARINA DENISKOVA, MD, PHD
JUNE 07, 2012, MILAN, I SEMINARI SSFA a cura del GdL Medicina Farmaceutica

Premier Research, solutions-driven CRO, provides premier people, premier process and premier performance for biopharmaceutical and medical device companies worldwide.
Today’s Topics

▪ What advantages do Russia and Ukraine offer?
▪ What bureaucratic and logistical challenges do we need to overcome?
▪ Which types of trials work best?
▪ How do we motivate enrollment and retention?
Ukraine
Clinical Trials in Russia and Ukraine

Sources: www.grls.rosminzdrav.ru, www.pharma-center.kiev.ua

*2010 data for Ukraine is only for first half of year
Clinical Trials in Russia

Source: www.grls.rosminzdrav.ru

*2012 data is only Q1 of the year
http://www.clinicaltrials.gov

Search in ClinicalTrials.gov with parameters:

**Hide studies that are not seeking new volunteers.**

**Hide studies with unknown recruitment status.**

**Results:**

- Found **2630** studies with search of: France | Open Studies | Exclude Unknown
- Found **2381** studies with search of: Germany | Open Studies | Exclude Unknown
- Found **1454** studies with search of: Italy | Open Studies | Exclude Unknown
- Found **498** studies with search of: Russia | Open Studies | Exclude Unknown
- Found **201** studies with search of: Ukraine | Open Studies | Exclude Unknown
Advantages to Russia and Ukraine

- Large and available patient population
  - Genetic diversity and high urban proportion
  - Availability of treatment-naïve patients
  - High motivation of patients and subject retention
  - Excellent patient compliance
  - High prevalence and incidence of all the major diseases
Advantages to Russia and Ukraine

Highly centralized healthcare system
Highly qualified, enthusiastic investigators
Legislation matches international standards and practice
Proven high quality clinical trial data

Source: FDA website; *Based on Letter Issued Date
Local Healthcare System - Russia

- Centralized, state governed

- Specialized medical centers in oncology, cardiology, endocrinology, pulmonary, neurology and other areas exist in all big cities

- Big number of physicians per capita - 42 per 10,000 in the country and about twice more in Moscow and Saint Petersburg

- Free medical care covers emergency medical care, ambulatory care and treatment in hospital

- Free of charge medication is provided to all Russian citizens in case of hospitalization and in emergency and ambulance situations

- Many diseases giving patients the right to obtain free medicines
Local Healthcare System - Russia

- The health care is insufficiently financed from the state budget
- 57% of patients are not satisfied with state medical care

There is a deficiency of modern medical equipment, free medication, and physicians providing for patient recruitment friendly environment
Local Healthcare System - Ukraine

- Public health care system is centralized, state governed
- High capacity: high numbers of physicians and beds
- Public healthcare in Ukraine is supposed to be free and cover emergency and primary medical care
- Private healthcare and insurance industry is also available
- Public healthcare reform is going to be started in 2014
Local Healthcare System - Ukraine

- Lack of modern medical facilities and free medicines
- Patients often have to pay for extras such as specialized equipment and procedures
- Patients are concentrated in large well-equipped hospitals with high capacity outpatient departments
- Wages of state employed doctors are relatively low

Excellent environment for patient recruitment and investigators motivation
Bureaucratic and Logistical Challenges

- Clinical trial authorization process
- Regulatory requirements and timelines
- Barriers related to customs with import of study medication and export of biological samples
- Contracting with hospitals

Need to work with experienced teams in the region
Start-up Process for Russia

- Document collection, translation and proofreading, site selection, obtain patient insurance policy, sponsor registration at the MoH
  - Submit CTA
  - Ethics Committee
    - Positive opinion
  - Ministry of Health
    - Positive opinion
  - Scientific Centre
  - CTA Approval
    - Import License IMP
    - Export License Biosamples
    - Contracts and Local EC approvals
  - Importation of IMP into Russia
    - Shipment of IMP and CTM to sites
      - Site Initiation
      - First Patient In

Typically 4.5 to 5 months
Start-up Process for Ukraine

Document collection, translation and proofreading, site evaluation and patient insurance policy selected

- CEC submission
- SEC submission
- CEC approval
- SEC and MoH approval

CTA Approval

- Import License IMP and CTM
- Export License Biosamples
- Contracts

Importation of IMP and CTM into Ukraine

Site Initiation

Site Evaluation

First Patient In

Typically 4.5 months
Start-up Process for Ukraine (new)

Document collection, translation and proofreading, site evaluation and patient insurance policy selected

- SEC submission
- SEC and MoH approval

CTA Approval

- Import License IMP and CTM
- Export License Biosamples
- Importation of IMP and CTM into Ukraine
- Shipment of IMP and CTM to sites
- Contracts and Local ECs Approvals

First Patient In

Site Initiation

4.5 ?? months
## Approval Process

<table>
<thead>
<tr>
<th>Requirements</th>
<th>Russia</th>
<th>Ukraine</th>
</tr>
</thead>
<tbody>
<tr>
<td>State authorities</td>
<td>National EC, Scientific Center, MoH</td>
<td>State Expert Center, MoH</td>
</tr>
<tr>
<td>Submission requirements (only final document versions are accepted for review and approval)</td>
<td>Web based and in person</td>
<td>In person only</td>
</tr>
<tr>
<td>Translations language</td>
<td>Russian</td>
<td>Ukrainian and Russian</td>
</tr>
<tr>
<td>Translations requirements</td>
<td>Entire study protocol and IB have to be translated</td>
<td>The only study protocol synopsis and special section from IB have to be translated</td>
</tr>
<tr>
<td>IMPD needed for the submission</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Clinical trial approval timelines</td>
<td>70 calendar days</td>
<td>60 ??? calendar days</td>
</tr>
<tr>
<td>Import licenses needed</td>
<td>IMP</td>
<td>IMP and CTM</td>
</tr>
<tr>
<td>Import License</td>
<td>Umbrella</td>
<td>For every shipment</td>
</tr>
<tr>
<td>Export license needed</td>
<td>Biological samples</td>
<td>Biological samples</td>
</tr>
<tr>
<td>License application needed can be done only upon written approval</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Issues with Approval Process

Russia

• Doubled submission process → through MoH website and personally in paper
• Low possibilities to control how the process of approval is going, no direct contact with scientific and ethics experts is allowed
• Additional application to the MoH after expertise
• Obtaining a paper approval is time consuming
• Very rarely does the approval process take 10 weeks as stated in the law, it can be double that amount (general but not Premier Research’s experience)
Issues with Approval Process

Ukraine

- Some of the regulatory requirements are unclear, inconsistent or excessive
- Clinical trial authorization process is a sort of bureaucratic and time-consuming
- Clinical trial authorization timelines is frequently prolonged due to deficiency/clarification letters
- Written approval issue and signing by MoH takes additional time
## Import/Export Considerations

<table>
<thead>
<tr>
<th>Import of Medical/Study Material</th>
<th>Export of Biological Samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cannot be sent directly to investigators must go to import license holder address</td>
<td>Must pass through customs</td>
</tr>
<tr>
<td>Must pass though customs clearance</td>
<td>Exported on behalf of holder of the export license and not the investigator</td>
</tr>
<tr>
<td>Complicated customs clearance procedure which requires involving of customs brokers</td>
<td>Holder of the export license has to provide the investigator with a package of signed documents which must accompany every shipment</td>
</tr>
<tr>
<td>Study supplies (devices) require certificates of compliance obtained in Russian Federation</td>
<td></td>
</tr>
<tr>
<td>Any material sent to investigators has to be reflected in accounting (study specific shipment form is not enough)</td>
<td></td>
</tr>
</tbody>
</table>
Overcoming the Challenges

- Prepare submission package thoroughly
- Book time and recourses for logistical tasks
- Remember that the most of reliable courier companies are not reliable customs brokers in Russia when we speak about clinical trials
- Use customs brokers experienced in customs clearance of clinical trials material
- Do not be frustrated if Russia and Ukraine are late with study approval and site initiation
Best Fit Trials for the Region

Russia
- Phase 2-3 studies
- Adult population
- Most major therapeutic areas

Ukraine
- Any phase that is well-designed with benefits and risks balancing
- Availability of standard and new mode treatment
- Most major therapeutic areas
Major Therapeutic Areas

Number of Clinical Trials from 2007-2009

<table>
<thead>
<tr>
<th>Therapeutic Area</th>
<th>Russia</th>
<th>Ukraine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>224</td>
<td>57</td>
</tr>
<tr>
<td>Neurology and Psychiatry</td>
<td>161</td>
<td>109</td>
</tr>
<tr>
<td>Oncology</td>
<td>313</td>
<td>95</td>
</tr>
<tr>
<td>Respiratory/Pulmonology</td>
<td>160</td>
<td>52</td>
</tr>
</tbody>
</table>

Sources: www.grls.rozminzdav.ru, www.pharma-center.kiev.ua
## Limitations in Russia

<table>
<thead>
<tr>
<th>Limitation</th>
<th>Exception</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pediatric study (up to 18 years)</td>
<td>Trial is necessary for strengthening children’s health or prevention of infectious diseases in children</td>
</tr>
<tr>
<td></td>
<td>Trial objective is to obtain data for better medication dosing in children</td>
</tr>
<tr>
<td></td>
<td>A trial on adults must precede the trial on children in all cases</td>
</tr>
<tr>
<td>IP is narcotic, psychotropic substances or their precursors</td>
<td>Import, logistic and handling limitation are possible</td>
</tr>
<tr>
<td>Phase 1 studies on healthy volunteers</td>
<td>Allowed only for local manufactures of IP</td>
</tr>
</tbody>
</table>
### Limitations in Ukraine

<table>
<thead>
<tr>
<th>Limitation</th>
<th>Exception</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pediatric study (under 18 years)</td>
<td>Clinical trials have to be designed to minimise pain, discomfort, fear and risk. No incentives or inducements are given except compensation in the event of a clinical trial-related injury</td>
</tr>
<tr>
<td>IP is narcotic, psychotropic substances or their precursors</td>
<td>Import, logistic and handling obstacles are expected</td>
</tr>
<tr>
<td>Phase 1 and bioequivalence studies</td>
<td>Allowed only at the healthcare institutions which are in compliance with the special requirements</td>
</tr>
<tr>
<td>Placebo-controlled studies</td>
<td>Studies with the placebo-control only are not welcomed</td>
</tr>
</tbody>
</table>
Enrollment and Retention

- Careful site selection
- Enrollment plans and milestones
- Patient prescreening
- Patient communication and referral
- Additional site and patient benefits
- Site management and motivation
Enrollment

Conservative strategies of patients’ recruitment work well
▪ Investigators invite their own patients to the trial
▪ Involve local doctors to send patients from other clinics
▪ Regular calls to the sites

What is used less frequently but still works well
▪ Involvement of backup sites
▪ Bonuses for inclusion of every new patient
▪ Advertisement through doctor-to-doctor letters, webs of patients’ and professional organizations, webs of clinics
Retention

What keeps patients in the study

▪ Cultural background - high level of confidence to the patient's physician
▪ Access to high qualified doctors and well equipped clinics
▪ Free modern treatment and comprehensive examination

What you can use

▪ Provide free rescue medication
▪ Reimburse transportation of patients
▪ Reimburse of telephone calls to investigators
▪ Awaiting room with tea and snacks during visits for PK samples
Patient recruitment is the #1 cause of clinical trial delays.

CenterWatch has reported that roughly 70% of all trials are delayed from one to six months due to patient enrollment problems.
Case Study: Metastatic Renal Cell Carcinoma

Sites in Russia started recruiting patients in Oct/Nov 2011
Case Study: Primary Immune Deficiency

Recent study in the Ukraine

<table>
<thead>
<tr>
<th></th>
<th>Planned</th>
<th>Actual</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of sites</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Duration of enrollment</td>
<td>6 months</td>
<td>3 months</td>
</tr>
<tr>
<td>Number of patients screened</td>
<td>25</td>
<td>16</td>
</tr>
<tr>
<td>Number of patients randomized</td>
<td>9</td>
<td>13</td>
</tr>
</tbody>
</table>
Summary

- Russia and Ukraine are very attractive regions to conduct clinical trials and achieve fast patient recruitment and low drop-out rate

- All key therapeutic areas are active and growing in the region

- ICH-GCP principles are continuously incorporated into local regulations
Questions?

Marina Deniskova, MD, PhD
Clinical Research Manager, Russia
marina.deniskova@premier-research.com

www.premier-research.com