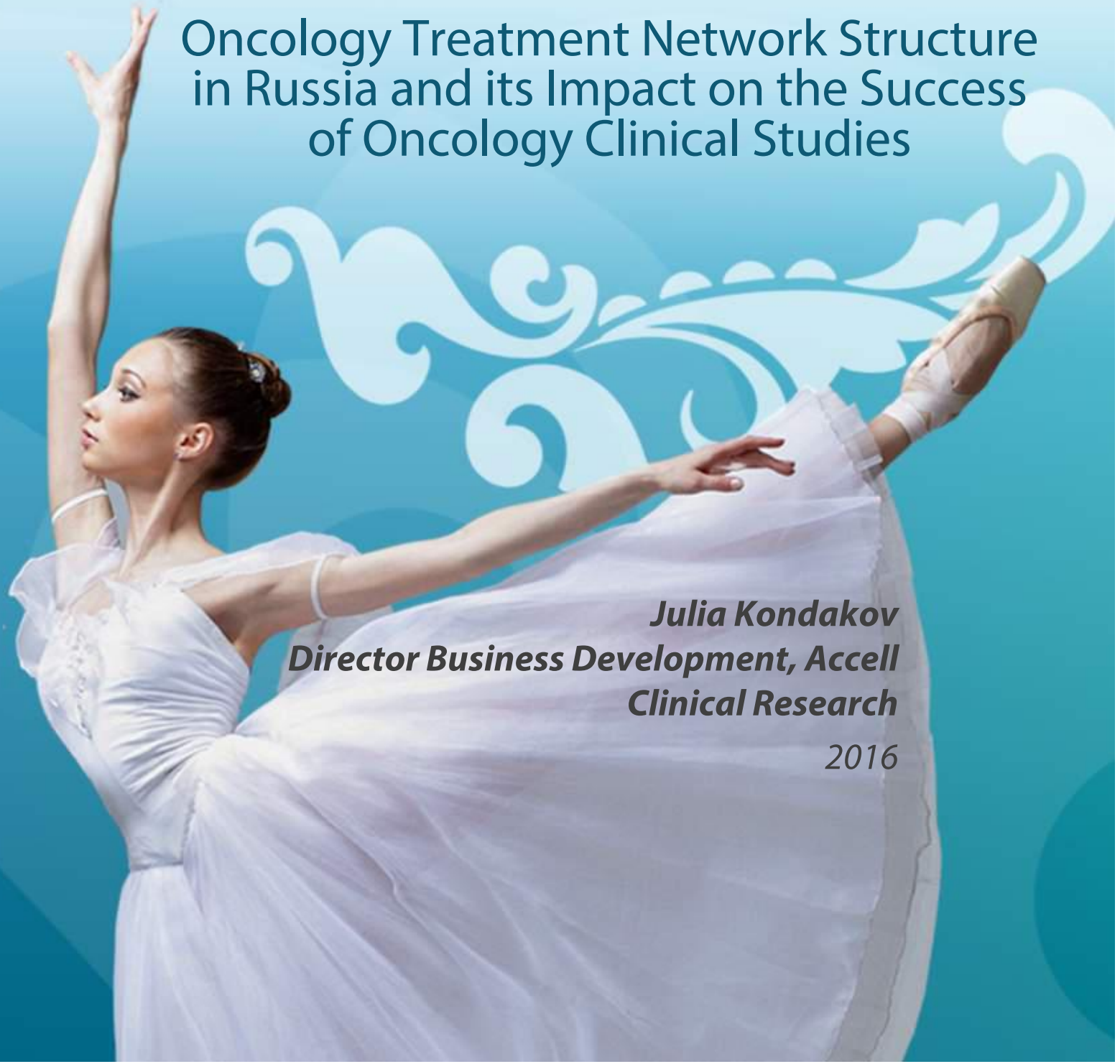
Accell
CLINICAL RESEARCH

COMMITMENT
TO EXCELLENCE

Oncology Treatment Network Structure in Russia and its Impact on the Success of Oncology Clinical Studies



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Case Study: Setting

- ✓ **Sponsor**: a biotech company developing their product for treatment of **Head & Neck Cancer** in a global **Phase III** clinical trial
- ✓ **Problem:** Slow recruitment globally, expected study delays
- ✓ **Clinical trial set-up:**
  - **First slate of countries**: USA, Canada, Belgium, UK
  - **Second slate:** additional 11 countries in Europe
- ✓ **Actions**:
  - After about 16 months with slow recruitment, **Russia** as emergency country was added
  - After all formalities and regulatory requirements were completed, **6 months remained for recruitment** in Russia

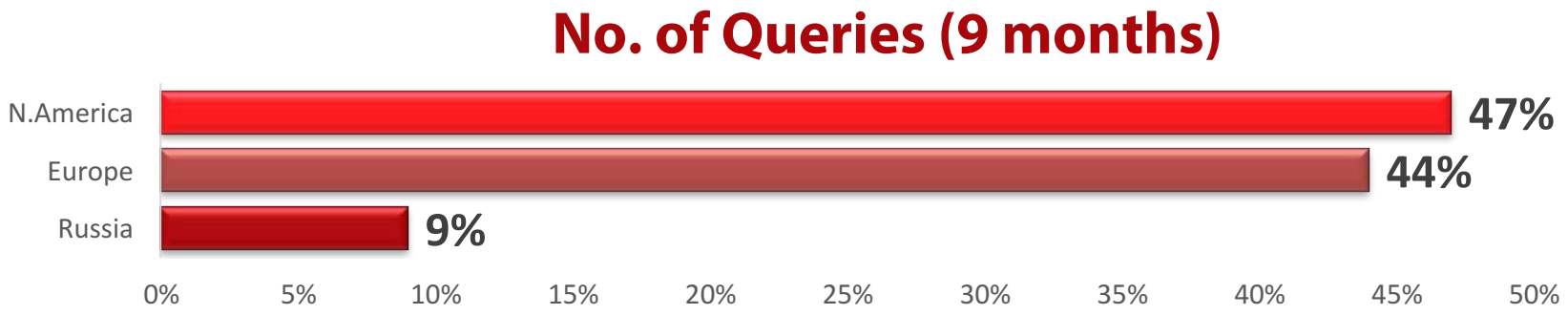
Case Study (cont'd): Patient recruitment

	North America	Western Europe	Russia
Enrollment period (months)	26	26	6
Active sites	14	32	10
Patients enrolled	32	99	36
Enrollment rate (pts/site/mo)	0.08	0.1	0.6

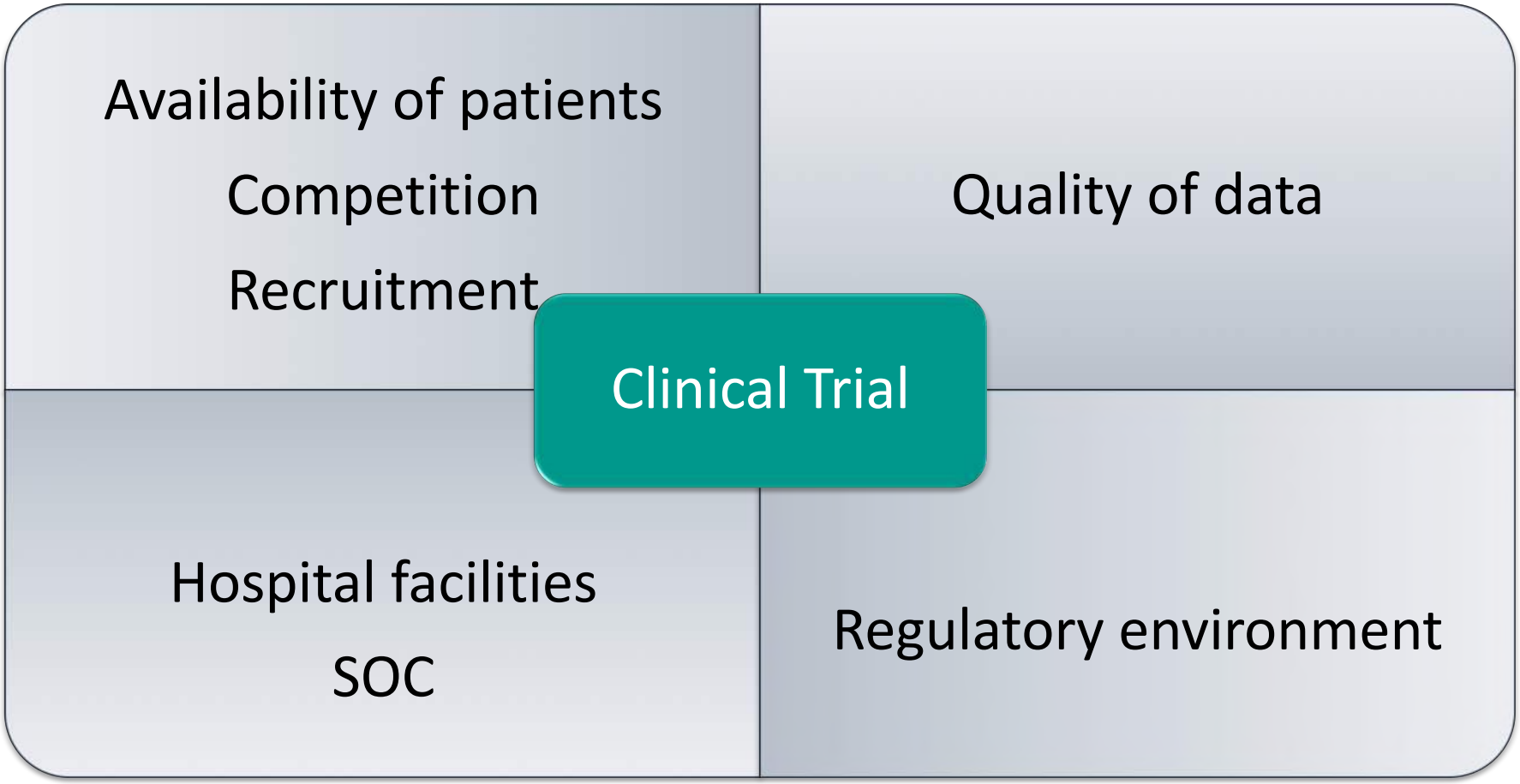
- Enrollment period in Russia was **only 23% of the total** enrollment period.
- Russia had **only 27% of sites globally**.
- The enrollment rate in Russia was **6 times higher** than in Europe and in North America
- Russia recruited **21.6 % of total patients in just 6 months**.

Case Study (cont'd): Queries

	Q1 Year 1		Q4 Year 1		Q1 Year 2	
	#	%	#	%	#	%
Russia	136	9.5	104	9.9	14	3.5
Europe	594	41.8	545	51.6	134	33.3
N.America	692	48.7	406	38.5	254	63.2



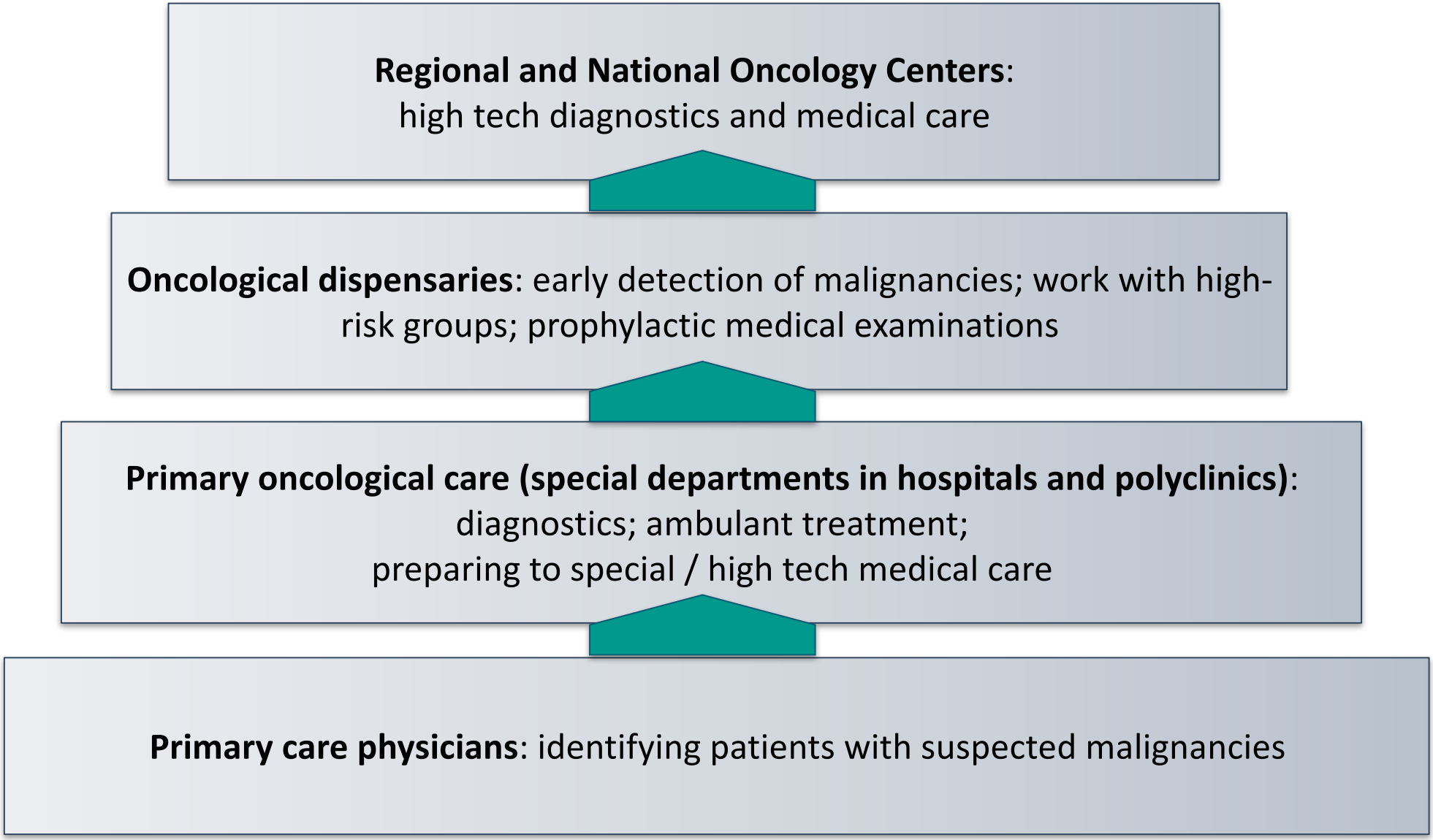
Oncology Trials: Main Issues



History of oncology care network

- ✓ Nationwide oncology agency founded in 1945
  - before that date, a lot was done to create a network of medical facilities for treatment of malignancies
- ✓ Russian Oncological Scientific Center n.a. N.N. Blokhin founded in 1951
  - currently, it's one of the major medical institutions in Russia and in the world
- ✓ 1990s — decline in healthcare
  - higher mortality due to malignancies
- ✓ 2009-2014 — established National Oncology Program
  - 47 bln RUR (~1,3 bln USD) investments

Multi-tiered centralized oncology care

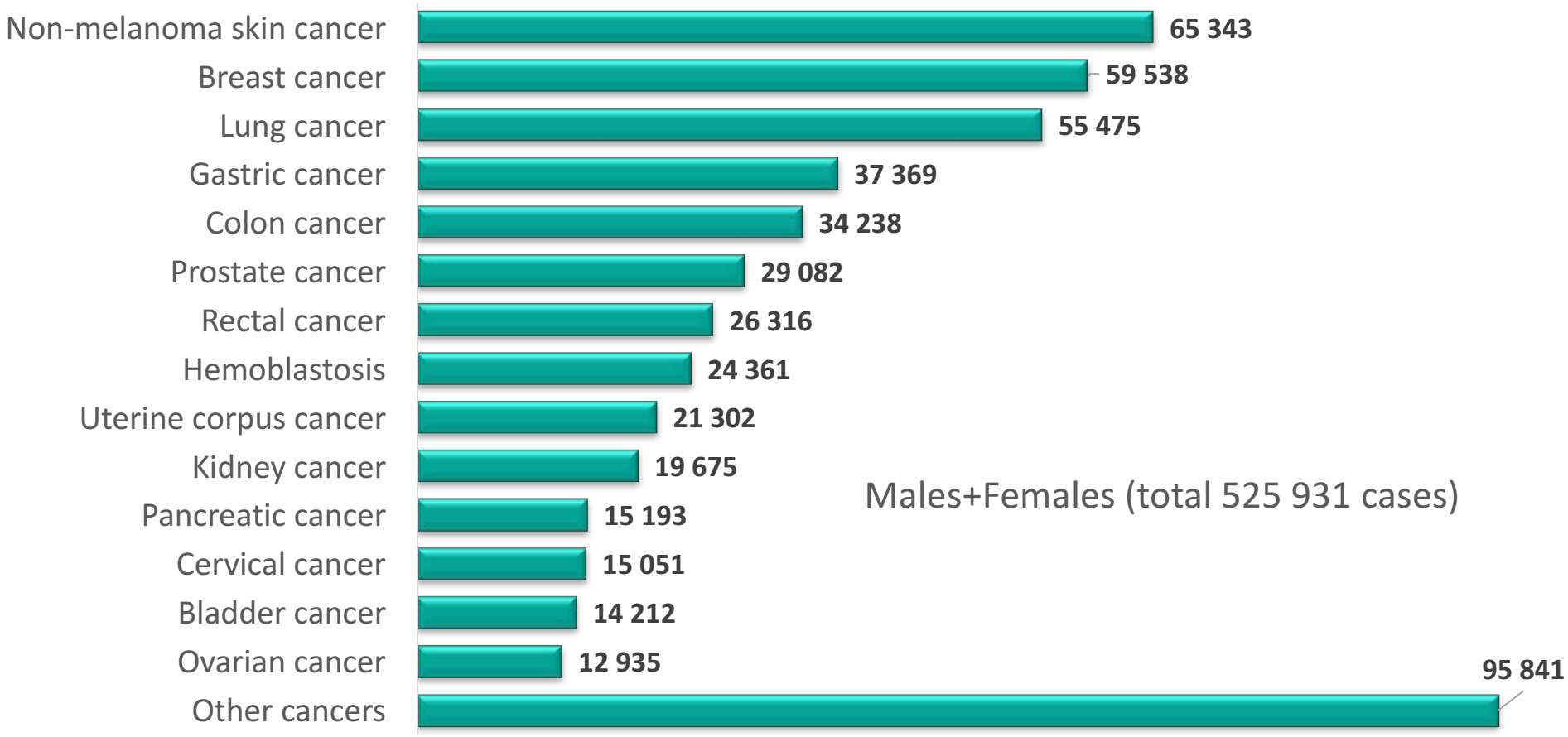


Limitations on treatment options for oncology disease

- ✓ 535 887 new cases in 2013 (~1 new case per minute!)
  - Incidence (2013): 374,2 cases per 100 000 vs. 234,7 world average
  - 41,6 % of cases diagnosed at III-IV stages (2014) *Sources: RBC, MNIOI*
- ✓ Since 2015, oncology treatment is financed from the federal Obligatory Medical Insurance funds
  - Very restricted finances
- ✓ In many therapeutic areas, the newest protocols of treatment are not available because they are not yet included into national standards of medical treatment
- ✓ In many cases treatment of oncology disease starts at more advanced stages of the disease
  - Weak early diagnostics
  - Long time spent to go through all bureaucracy to get treatment

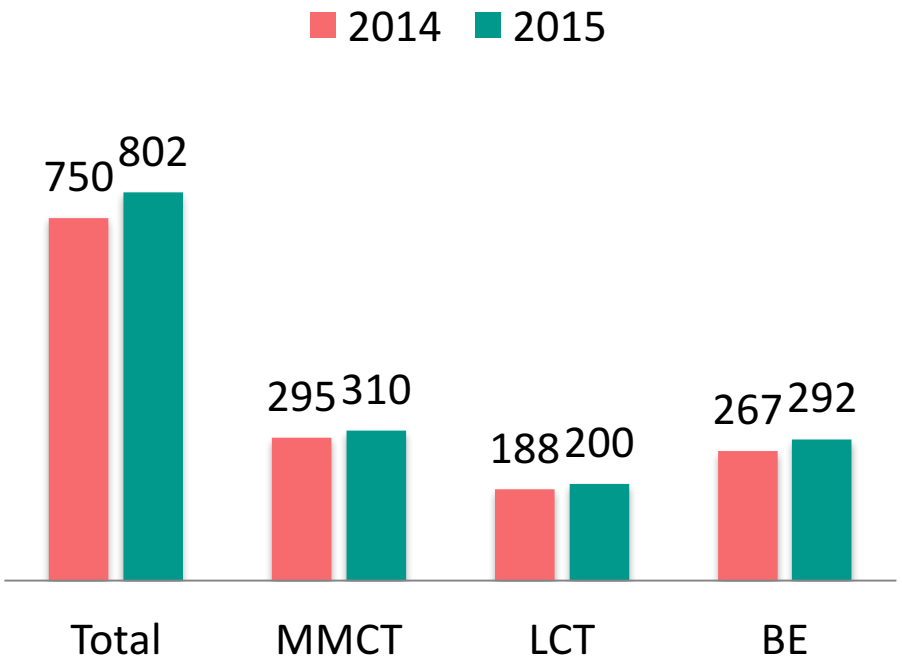
New Cancer Cases in 2012

Total population 145 million



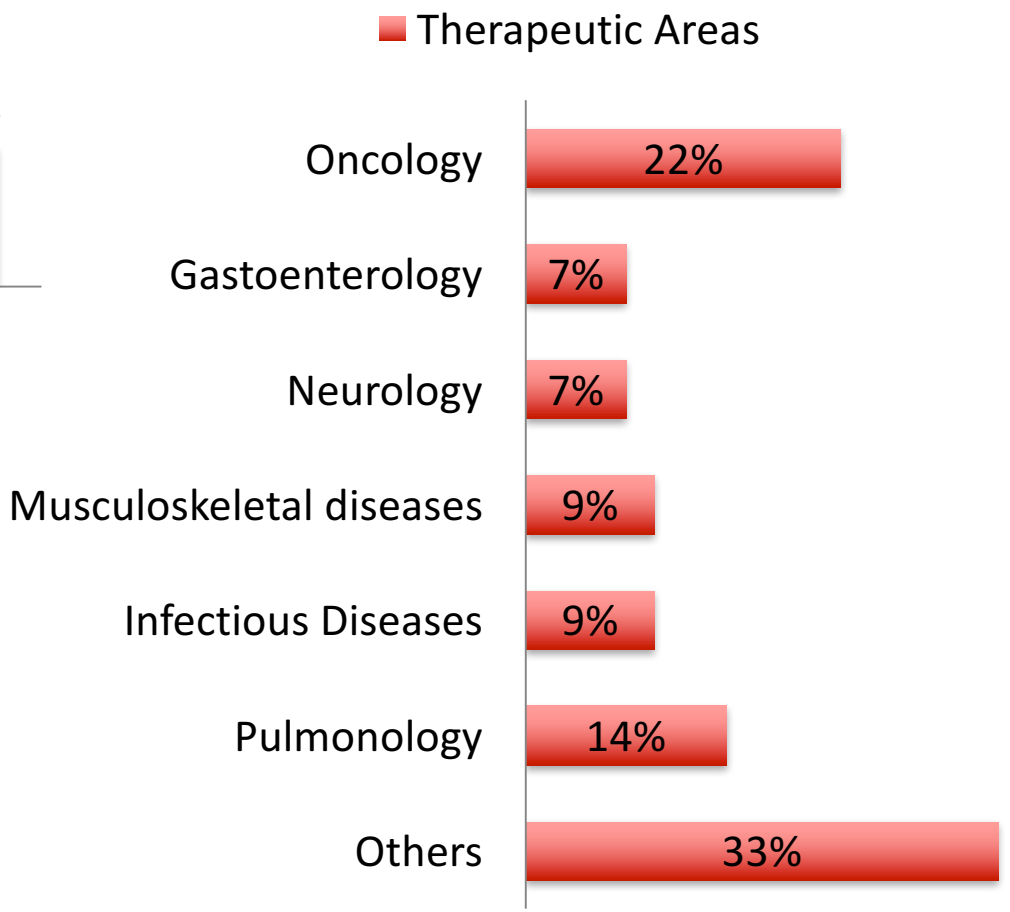
Source of data: Malignancies Statistics in Russia and CIS, 2013 / ed. by M.I. Davydov, Dr. E.M. Aksel

New clinical trials approvals in 2014-2015



Phase II – 16%
Phase III – 69%
(2015)

Therapeutic Areas



Clinical Oncology Trials in Russia: Strong Side — Competition

- ✓ 109 new clinical studies in oncology initiated in 2015
  - Increase from 89 in 2014
- ✓ While the landscape is competitive for oncology at the largest institutions, the opportunities for recruitment are plentiful
  - Russian Scientific Oncology Center n/a N.N.Blokhin initiated 74 studies
- ✓ Relatively few trials competing for resources and patients at sites
- ✓ Regional sites are likely to be high recruiters as they receive fewer studies than centrally located sites; quality and experience remain on par with the worldwide standards

Source of data: Clinical Trials in Russia Orange Paper Annual 2014; Synergy Research Group

Clinical Oncology Trials in Russia: Strong Side — High Quality of Data

- ✓ Qualified and experienced investigators
  - PI must have at least 5 years of experience by law
  - experienced study nurses
  - experience with different agents, including biologicals
- ✓ Attentive documents completion
  - at many sites — dedicated staff, including coordinators,
  - no issues with internet access
  - experience with the e-CRFs
  - variety of trainings to ensure understanding of all requirements
- ✓ Investigational sites with experience in conducting industry-sponsored, ICH-GCP compliant clinical studies
- ✓ Regulatory authorities conduct periodic inspections of clinical studies

Oncology Clinical Trials in Russia: Facilities and SOC

National Oncology Program

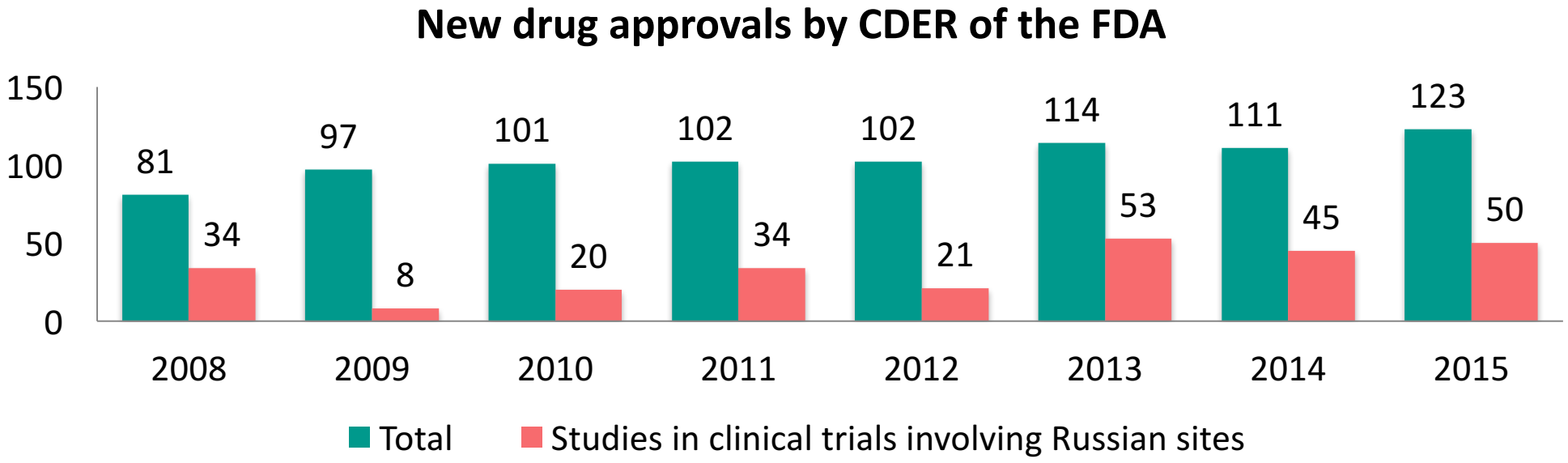
- ✓ 47 bln RUB (~1,3 bln USD) investment in 2009-2014
- ✓ 101 new medical facilities built
- ✓ 389 000 units of medical equipment purchased and installed, incl.:
  - 700+ tomographs (CT, MR)
  - 6 500 units of X-ray and angiography equipment
- ✓ In many indications the SOC are the same as widely accepted in the Western countries (EU/USA)

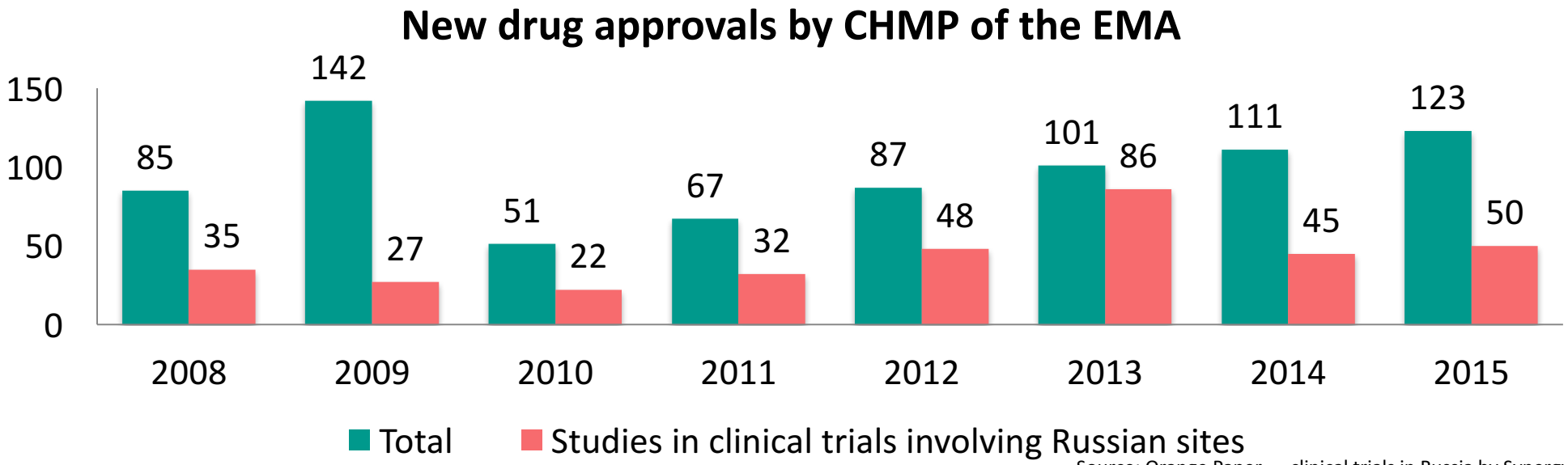
Sources: kommersant, mednovosti

Source: http://oncocentre.ru/

Source: http://rrcrst.ru/

Data from Russian sites: FDA & EMA Acceptance



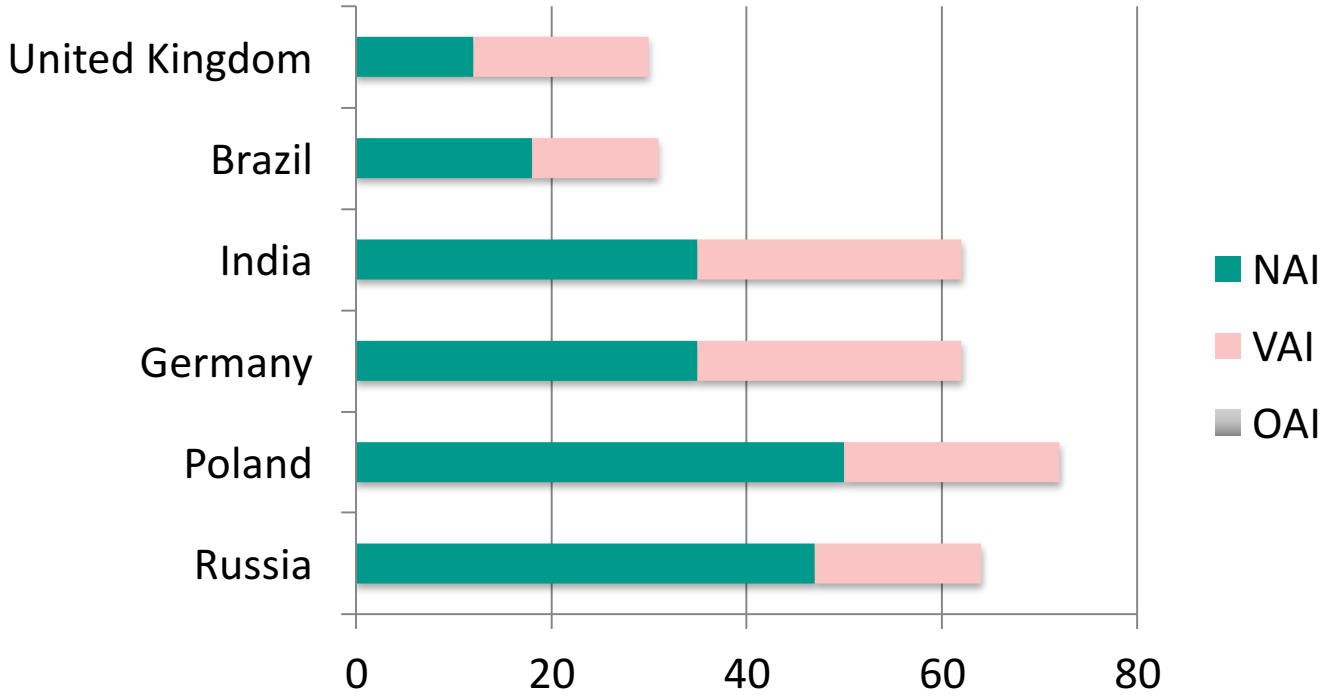


Source: Orange Paper — clinical trials in Russia by Synergy

"Most of the data from pivotal clinical trials submitted for marketing authorization applications to the EMA are from third countries and the **Russian Federation (RF) is one of the key players in this respect**. In fact about 60 per cent of all clinical trial data included in MA applications to the EMA has been generated outside the EU…."

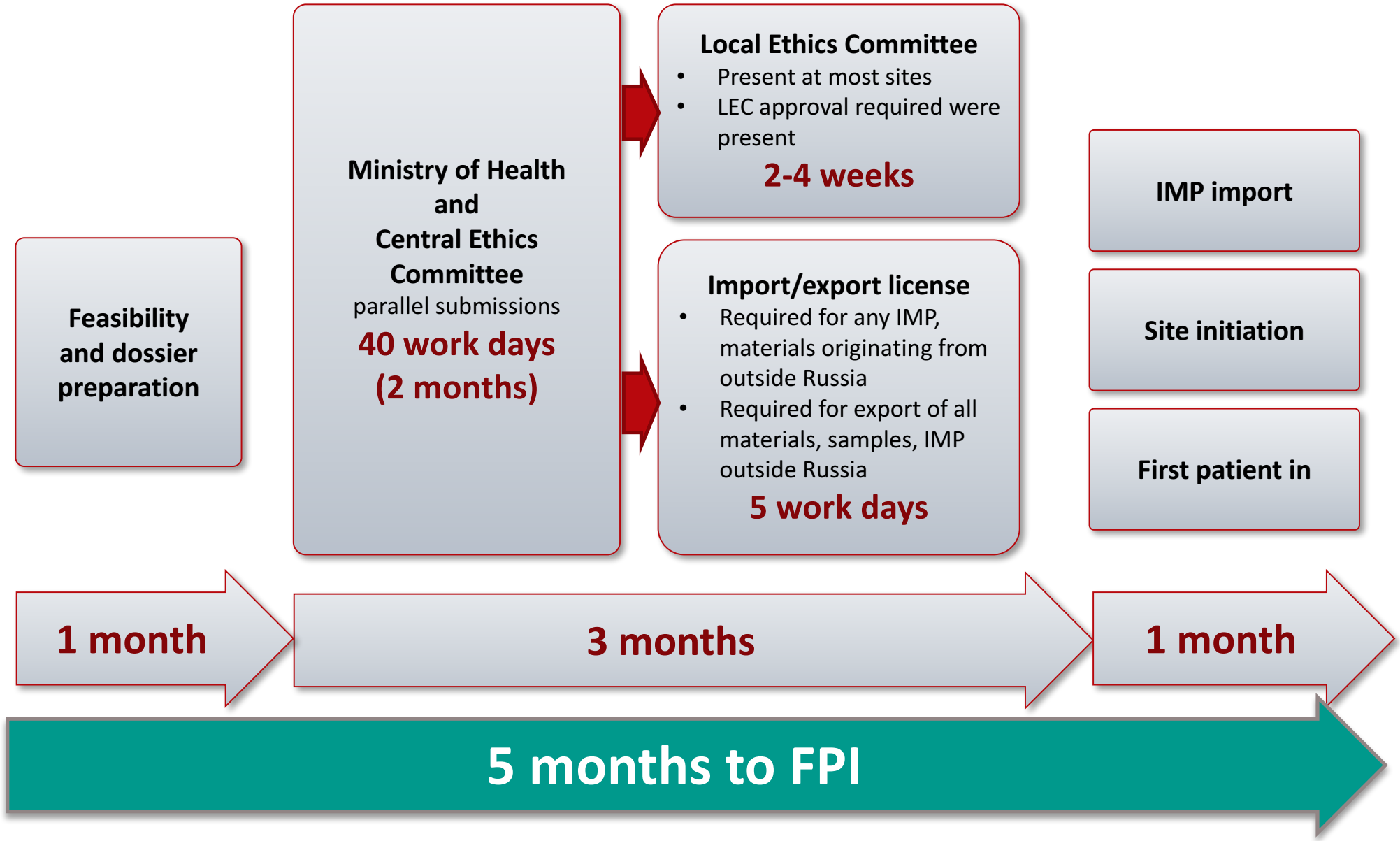
European Commission Analytical Report - Cooperation in the field of clinical trials, September 2012

Clinical Investigator Inspections, FDA (2008-Q1 2016)



http://www.accessdata.fda.gov/scripts/cder/CLIIL/index.cfm

Start-up timelines for Phase I-III



Perceived challenges

Myth

- ✓ Difficult logistics
  - Closed borders
  - Long wait at customs
  - Lack of transparency
- ✓ Language barriers
  - Communication with PI
  - Communication with CRO
  - Translation requirements
- ✓ Quality and Compliance
  - At site
  - Data acceptance by international regulators
- ✓ Regulatory system not meeting international standards

Fact

- ✓ Similar to other countries
  - Border control, not barriers
  - 3 days
  - Clear requirements, ask CRO
- ✓ Yes, different language
  - Working knowledge of English
  - English, communication plan
  - Taken care of by CRO
- ✓ Proven quality
  - FDA inspected
  - RZN inspected** – 101, 34 AI
  - New drug approvals with Russian data
- ✓ In-depth analysis of Russian regulatory framework undertaken by European Commission during covering legislation up to 2012.

*2015, ** 2008-2014

“Cooperation in the Field of Clinical Trials”, September 2012

Conclusion:
“In general, it can be stated that for the conduct and supervision of clinical trials in the EU and the RF equivalence of the respective regulatory/legislative framework provisions is given. However, a number of differences exist….”

Clinical trials involving healthy volunteers, i.e. in phase I studies, with “medicinal products manufactured outside the RF” are prohibited, but for local sponsors are permitted. **Also phase I studies with foreign drugs involving patients are possible**

Clinical sites for conducting clinical trials need to be accredited by the MHSD (Ministry of Health and Social Development)

(Principal) investigators must have **a 5-year experience** in the conduct of clinical trials in order to be eligible as investigator in a clinical trial

The law provides very strict rules concerning the conduct of clinical trials on defined vulnerable persons, **exceeding those in E**U

http://ec.europa.eu/health/files/international/report_clinical-trials__sept2012.pdf

Clinical Trials in Russia: Summary

- Fast start-up
- Centralized healthcare, specialized hospitals
- Low migration rates, thus high retention
- Lower access to state-of-the-art treatment protocols
- Treatment-naïve patients in many indications
- Experienced and qualified investigators
- GCP incorporated in legislation

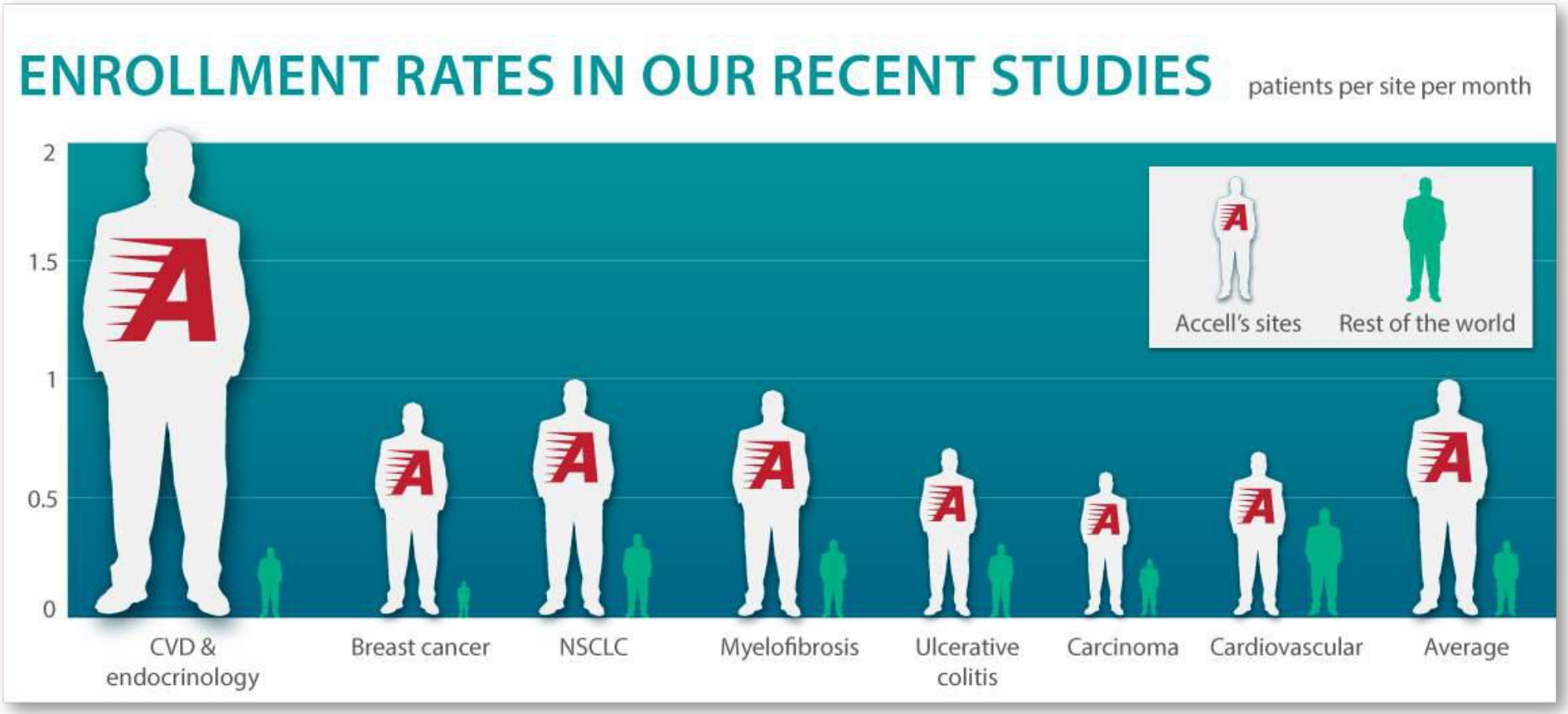
Faster recruitment

In our recent clinical studies, **enrollment rates** at Accell's sites were **1,4 to 7 times higher** than in the rest of the world

High quality of data

At least 30-40% lower per patient costs in oncology studies compared to Western countries and the US

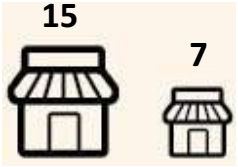
Clinical Trials in Russia: Fast Recruitment



Case Study – current study: Head & Neck / Cervical Cancer

Period of enrollment: 2,5 months (01 Sep 2015 — 15 Nov 2015)

Number of sites initiated within 2 months



Russia — 15
USA — 7

Enrollment

	Head & neck cancer cohort			Cervical cancer cohort		
	No. of patients	% of total	Enrollment rate (pts/site/month)	No. of patients	% of total	Enrollment rate (pts/site/month)
Total	21	100 %	0,37	12	100 %	0,21
Russia	**20**	**95 %**	**0,53**	**12**	**100 %**	**0,32**
USA	1	5 %	0,06	0	0 %	0

Conclusions - planning for success

- ✓ **Location**: Carefully assess available options for locations of your clinical trials

- ✓ **Availability** of
  - patients
  - SOC
  - acceptability of data by regulators
  - past performance

- ✓ **Look wider** towards regions that may be underutilized as a clinical study region, but offer great opportunities: Russia is a good example

Conclusions - planning for success

- ✓ **Backup plan**: Include more countries in your feasibility and budget process than you plan to initiate: in many cases having a backup selection of locations will save time and costs

- ✓ **Flexibility:** Your initial plans may change based on feasibility feedback and cause you to reconsider your country selection strategy

QUESTIONS?

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