Poster presented at DIA 2017

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Searching the registries for trial submission QA and competitor intelligence - Comparing ClinicalTrials.gov and EudraCT

Objective

Organizations conducting trials in the US and the EU submit trial information to both registries. Each authority requests some unique information, but much of the key information is common to both. We wanted to see how often there would be differences in the information available from both about the same trial.

Introduction

Do searches of clinical trial registries reveal differences in how the same trial is entered in different countries? Can registry searches help a company identify discrepancies in how a trial has been entered in different countries? And might these discrepancies mean richer competitor intelligence?

Method

We searched both NIH ClinicalTrials.gov and European Union EudraCT registries for a set of checkpoint inhibitor drugs, tremelimumab and pembrolizumab (Keytruda), using the same search terms. Searches were conducted in January 2017. Current content may not reflect these results.

	Total Records	Total Trials	Trials found in both registries
Tremelimumab	208	98	23
Pembrolizumab	783	426	62

The records retrieved were combined into a separate report for each drug. We compared the content of records from both registries for the same trial. Here we looked at three fields found in both registries: drug names, sponsors, and countries.

Identify Common Trial IDs

Records were considered to be about the same trial if they included at least one shared trial identifier found using the "Identify Common Trial ID" tool.

Pivotal to this analysis is the ability to quickly identify which records cover the same clinical trial. Each registry allows for additional trial identifiers to be included in the record. However matching records manually can be difficult, given that records don't always include the trial identifier for the other and formatting is inconsistent.

BizInt Smart Charts for Clinical Trials includes the Identify Common Trial IDs tool which automatically compares trial identifiers in a combined set and accounts for format differences. Records identified as linked are assigned a common trial id, which will be the NCT number if available.

	Common Trial ID	Trial Identifier	Database
1	NCT02142738	3475-024 2014-000323-25 142728 NCT02142738	ClinicalTrials.Gov
2	NCT02142738	EudraCT 2014-000323-25 MK-3475 versus SOC in 1L Subjects with PD-L1 Strong Metastatic NSCLC MK-3475-024	EUDRA Clinical Trials
3	NCT02562625	CCR 4251 NCT02562625	ClinicalTrials.Gov
4	NCT02562625	EudraCT 2014-004065-25 The PERM Study CCR4251	EUDRA Clinical Trials
5	NCT02819518	3475-355 2016-001432-35 163422 NCT02819518	ClinicalTrials.Gov
6	NCT02819518	EudraCT 2016-001432-35 A Phase III Study of Chemotherapy ± Pembrolizumab in 1L Triple Negative Breast Cancer MK-3475-355	EUDRA Clinical Trials

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Results

Table 1. Percentage of records with differing information in ClinicalTrials.gov and EudraCT for the same trial.

	Drug name	Sponsors	Countries	Any of these 3
Tremelimumab	30.43%	34.78%	73.91%	82.61%
Pembrolizumab	45.16%	24.19%	75.81%	93.55%

Differences in drug name could mean using a lab code versus a generic name, but also included cases where a drug was found in one record only. For one phase 3 trial EudraCT records didn't list one comparator drug, temozolomide, though it was in the trial title.

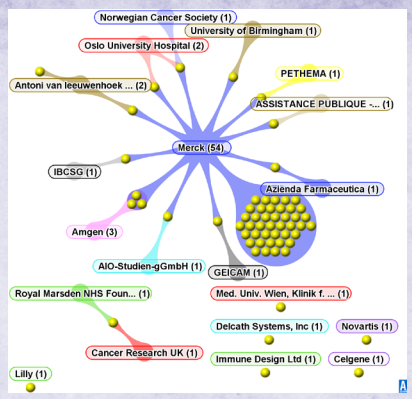
Sponsor and country differences always meant additional sponsors or countries in some records. ClinicalTrials.gov records were found with commercial sponsors not referenced in EudraCT. In one phase 2 trial, Pfizer was listed in the US record, but the EudraCT record listed no commercial sponsor. In another set of trials, US records listed AstraZeneca and EudraCT listed Pfizer.

EudraCT records in 4 trials listed only one country. For a phase 2 trial the US was listed as a location in EudraCT only. For a given trial, records from both registries included countries not found in other records.

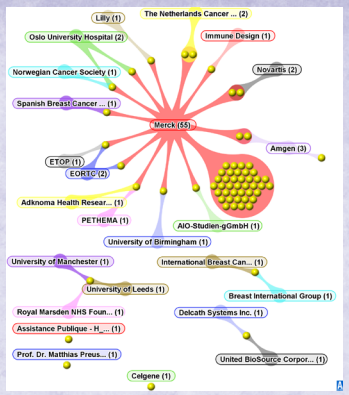
All trials listed different trial identifiers in the two sources, making identifying records for a trial in both registries problematic. For 43% of trials no records included the identifier for the other registry. Two trials found in EudraCT and 73 trials in ClinicalTrials.gov could not be matched to the other registry based on trial identifiers listed. Of the trials found only on ClinicalTrials.gov, 10 listed European countries. One was a phase 3 trial with a EudraCT number listed but the trial was not found searching EudraCT.

	Common Trial ID	Database	Drugs	Countries	Sponsor(s)
1	NCT02129556	ClinicalTrials.Gov	MK-3475	Australia Austria Belgium France Italy	International Breast Cancer Study Group Breast International Group
2	NCT02129556	EUDRA Clinical Trials	MK-3475 Herceptin	Austria Australia	International Breast Cancer Study Group (IBCSG) Merck Sharp & Dohme Corp.,
3	NCT02129556	EUDRA Clinical Trials	N/A Herceptin	Belgium Australia	International Breast Cancer Study Group (IBCSG) Merck Sharp & Dohme Corp.,
4	NCT02130466	ClinicalTrials.Gov	Pembrolizumab Dabrafenib Trametinib	Australia Denmark Israel Italy New Zealand United States	Merck Sharp & Dohme Corp. Novartis Pharmaceuticals
5	NCT02130466	EUDRA Clinical Trials	MK-3475	Denmark Australia Canada Israel Italy New Zealand United States	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc
6	NCT02492568	ClinicalTrials.Gov	pembrolizumab	Netherlands	The Netherlands Cancer Institute Merck Sharp & Dohme Corp.
7	NCT02492568	EUDRA Clinical Trials	MK3475	Netherlands	Stichting Het Nederlands Kanker Instituut-Antoni van Leeuwenhoek Ziekenhuis
8	NCT02883556	ClinicalTrials.Gov	Pembrolizumab		Assistance Publique - Hôpitaux de Paris
9	NCT02883556	EUDRA Clinical Trials	Pembrolizumab	France	ASSISTANCE PUBLIQUE - HOPITAUX DE PARIS (AP-HP) MERCK Sharp and Dohme

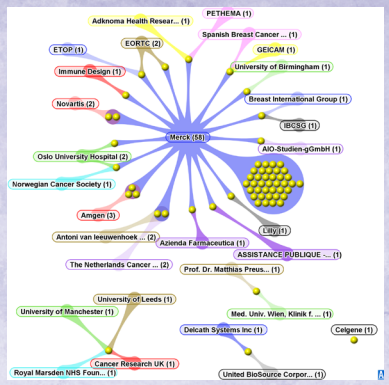
Trial Sponsors EudraCT



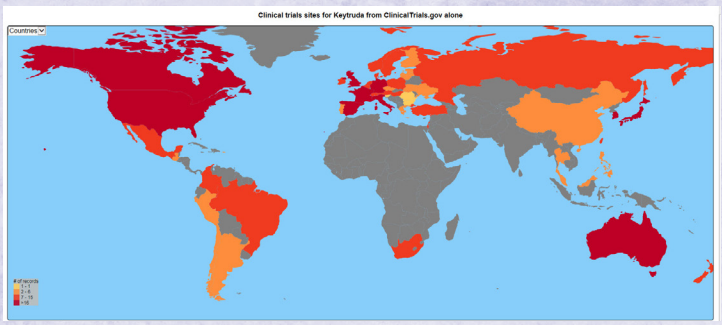
Trial Sponsors ClinicalTrials.gov

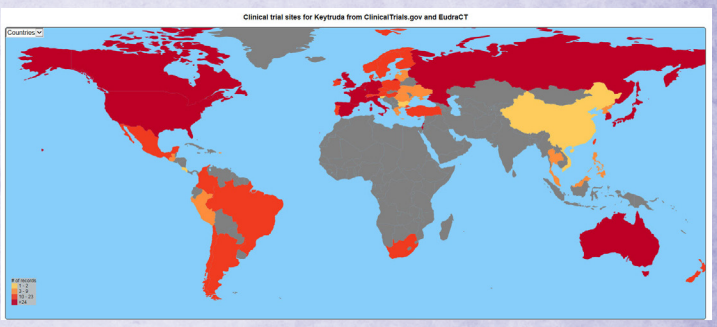


Trial Sponsors both sources

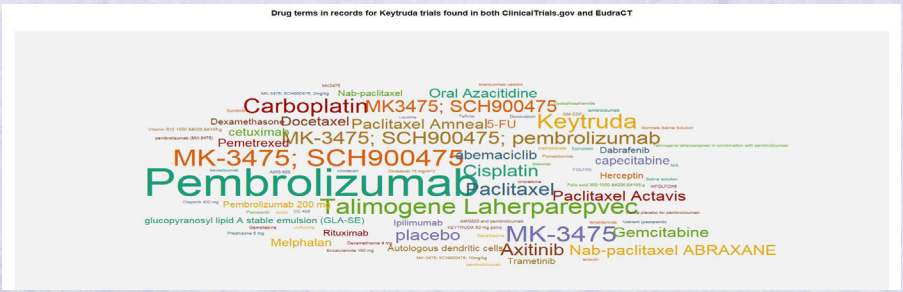


Combining data from both US and EU registries helps to connect the dots. Each source identifies around the same number of trials as Merck sponsored. But, it isn't the same set of trials, so the combination yields 58 trials with Merck sponsorship. Each source also identifies additional sponsors for those Merck trials. ClinicalTrials.gov notably shows Novartis and Lily as co-sponsors.





Adding EudraCT to ClinicalTrials.gov provides a more detailed picture. Here three countries were indicated as pembrolizumab trial sites only in EudraCT records: Costa Rica, Slovenia, and Vietnam. The combined data also shows a much clearer picture of global site selection for Keytruda: solid coverage in US, Canada, Central Europe, Russia, Australia, and Japan. The map sourced only from ClinicalTrials.gov is less clear: mixed coverage in the EU, Russia on a par with Mexico, and China on par with Argentina and Peru.



Common Trial ID	Database	Drugs	
NCT02014636	ClinicalTrials.Gov	Pazopanib	4.1
		MK-3475	4.1
	EUDRA Clinical Trials	Votrient (pazopanib)	4.2
		lambrolizumab	4.2
NCT02129556	ClinicalTrials.Gov	MK-3475	5.1
	EUDRA Clinical Trials	N/A	5.2
		Herceptin	5.2
	EUDRA Clinical Trials	MK-3475	5.3
		Herceptin	5.3
NCT02130466	ClinicalTrials.Gov	Pembrolizumab	6.1
		Dabrafenib	6.1
		Trametinib	6.1
	EUDRA Clinical Trials	MK-3475	6.2

This word cloud built with intervention terms for pembrolizumab trials from both registries shows the range of drug synonyms present.

By reviewing records for individual trials we can see how different the registries can be. Some individual EudraCT records may not mention our drug of interest at all.

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Conclusions

These results have implications from both a regulatory and a competitive standpoint. As we talk about harmonisation and as both registries are accessible to a global audience, the content presented on a company's trials should be the same. Review is needed to ensure that a company's submissions to either registry don't contain additional or different information.

From a competitive standpoint, the differences offer a competitive advantage when you search multiple sources and integrate information into your review. Rather than simple duplicates, information in records about the same trial can be quite different in the two registries. This can be key individual details, such as additional corporate trial sponsors or additional countries as trial locations. These differences can be counter-intuitive: some trials had European countries listed only in ClinicalTrials.gov and some trials had US listed as a location only in EudraCT records.

Here we looked at only three fields. Given our findings it seems likely that useful differences will be found in other areas as well such as endpoints and eligibility criteria. Taken together records for both sources can contribute to a clearer competitive landscape.

BizInt Smart Charts for Clinical Trials

To obtain the data for this analysis I needed to be able to import EudraCT data, available for download only as text, as well as ClinicalTrials.gov, where one of the fields included in this analysis is available only in the full XML export. To perform the necessary comparison, I needed to be able to identify which records covered the same trial. And I needed tools to easily review comparable content from each registry as record structure and terminology can be very different.

BizInt Smart Charts for Clinical Trials is the software used for this analysis, designed specifically for clinical trial data. The software builds a tabular report directly from the data formats available from each registry. While we could have selected other aspects of the trial for display, here we chose the three fields we analyzed for this poster: drug name, sponsors, and countries.

Using the Combine tool a single table was created combining records from both registries with a single column for each of the three selected fields: drug name, sponsors, and countries. The tool automatically maps comparable content from the two registries to the same column.

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