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Shaping the Future
of Drug Development

Synthetic Controls In Clinical Trials

When is it appropriate to use a SCA?

Rare disease	As disease understanding improves and diseases become sub-stratified they can effectively become "rare" diseases
Difficult Recruitment	Fear of being enrolled to a control treatment is a major determinant of non-participation in clinical trials[1]
Treatment Switching	E.g. NCT00428597: sunitinib vs. placebo in pancreatic cancer; median PFS at interim analysis was 11.4 vs. 5.5 months (HR = 0.42); 69% of patients crossed-over after interim analysis[2]
Ethical Concerns	Breakthroughs can challenge notions of clinical equipoise. E.g. drug targets an established driver, was studied within a population that has the driver, there are no major safety concerns, extremely high remission rates in early phase trials[3]

[1] Gaddipati H, Liu K, Pariser A, Pazdur R. Clin Cancer Res 2012; 18: 5172-5178. [2] Raymond E, Niccoli P, Castellano D, et al. J Clin Onc 2016 34:4_suppl, 309-309. [3] Sharma MR, Schilsky RL. Nat Rev Clin Oncol. 2012;9(4):208.

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For further details

Clinical Epidemiology

Dovepress

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REVIEW

Synthetic and External Controls in Clinical Trials – A Primer for Researchers

This article was published in the following Dove Press journal:
Clinical Epidemiology

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Abstract: There has been a rapid expansion in the use of non-randomized evidence in the regulatory approval of treatments globally. An emerging set of methodologies have been utilized to provide greater insight into external control data used for these purposes, collectively known as synthetic control methods. Through this paper, we provide the reader with a set of key questions to help assess the quality of literature publications utilizing synthetic control methodologies. Common challenges and real-life examples of synthetic controls are provided throughout, alongside a critical appraisal framework with which to assess future publications.

Keywords: synthetic control, RCTs, real-world evidence

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Text Rich Checklist

Table 1 Synthetic Control Quality Checklist

Item Number	Key Question	Criteria for Judgement
External Control Data Sources		
1	Was the original data collection process similar to that of the clinical trial?	State whether patients are from large well-conducted RCT(s) or high-quality prospective cohort studies, and whether patient characteristics are similar to the target population
2	Was the external control population sufficiently similar to the clinical trial population?	State how the external population is similar with regards to key characteristics, such as (but not limited to): age, geographic distribution, performance status, treatment history, sex etc.
3	Did the outcome definitions of the external control match those of that clinical trial?	State whether the outcomes are measured similarly or not
4	Was the synthetic control data set sufficiently reliable and comprehensive?	State whether there is sufficient sample sizes and covariates that can create comparable control groups
5	Were there any other major limitations to the dataset?	State any other potential limitations of the dataset that would limit the reliability and validity of comparisons
Synthetic Control Methods		
6	Did the clinical trial include a concurrent control arm, or is the synthetic control data the only control data?	State the size of the concurrent control arm and whether the external data set is the only dataset being used or is being used to complement concurrent control arm(s)
7	How was the synthetic control data matched to the intervention group?	State the analytical method(s) – eg propensity matching scores – used to create the synthetic control arm
8	Were the results robust to sensitivity assumptions and potential biases?	State whether the sensitivity analyses were undertaken or reasons for not conducting sensitivity analyses, and compare whether the sensitivity analyses were comparable to the primary analyses.
9	Were synthetic control comparisons possible for all clinically important outcomes?	State if all clinically important outcomes were considered for analyses. If not, state justifications for not including all important outcomes
10	Are the results applicable to your patients?	State whether the synthetic control group created are similar to the patient group of interest
11	Were there any other major limitations to the synthetic control methods?	State any other potential limitations of the statistical methods that would limit the reliability and validity of comparisons

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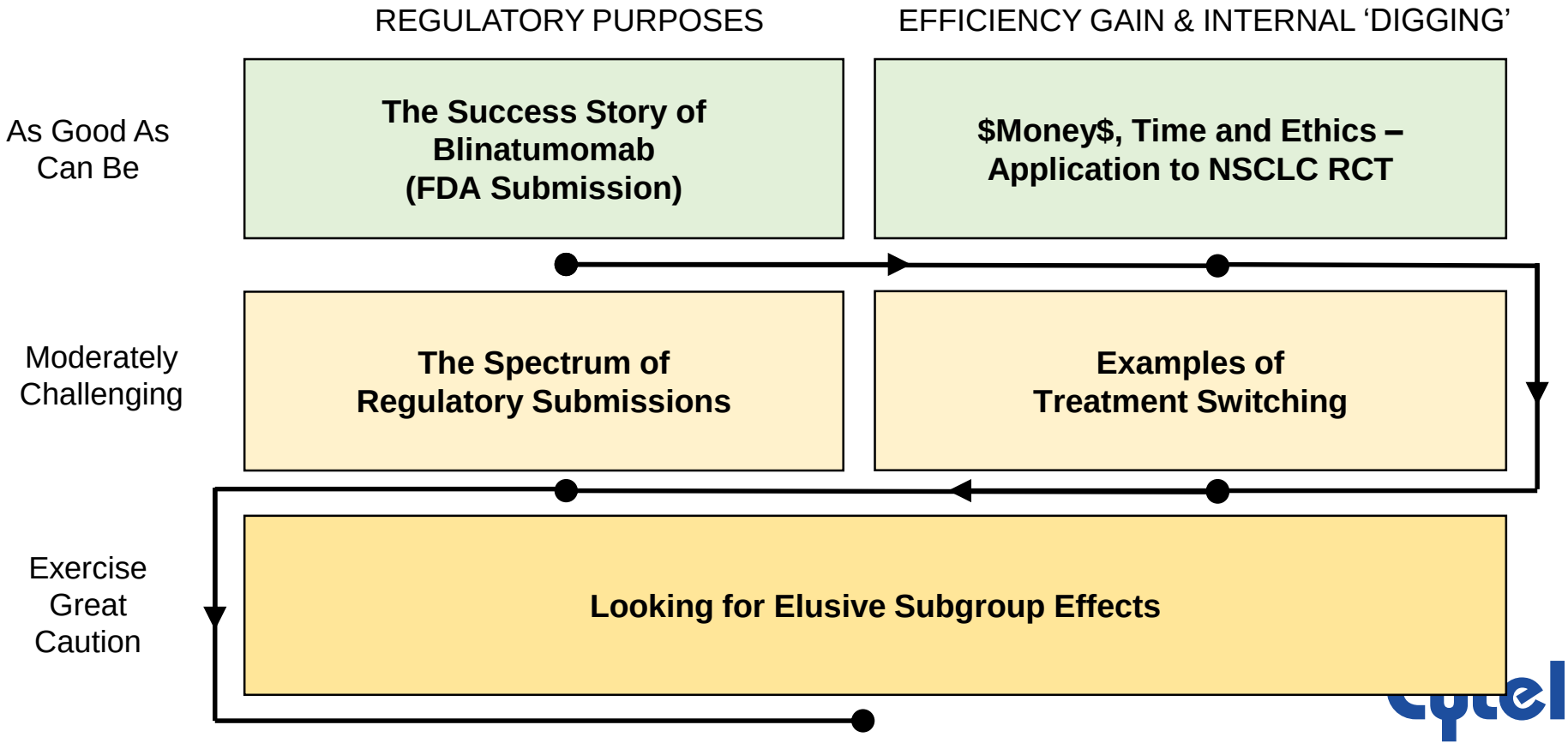
• Non-Bullet Point Outline



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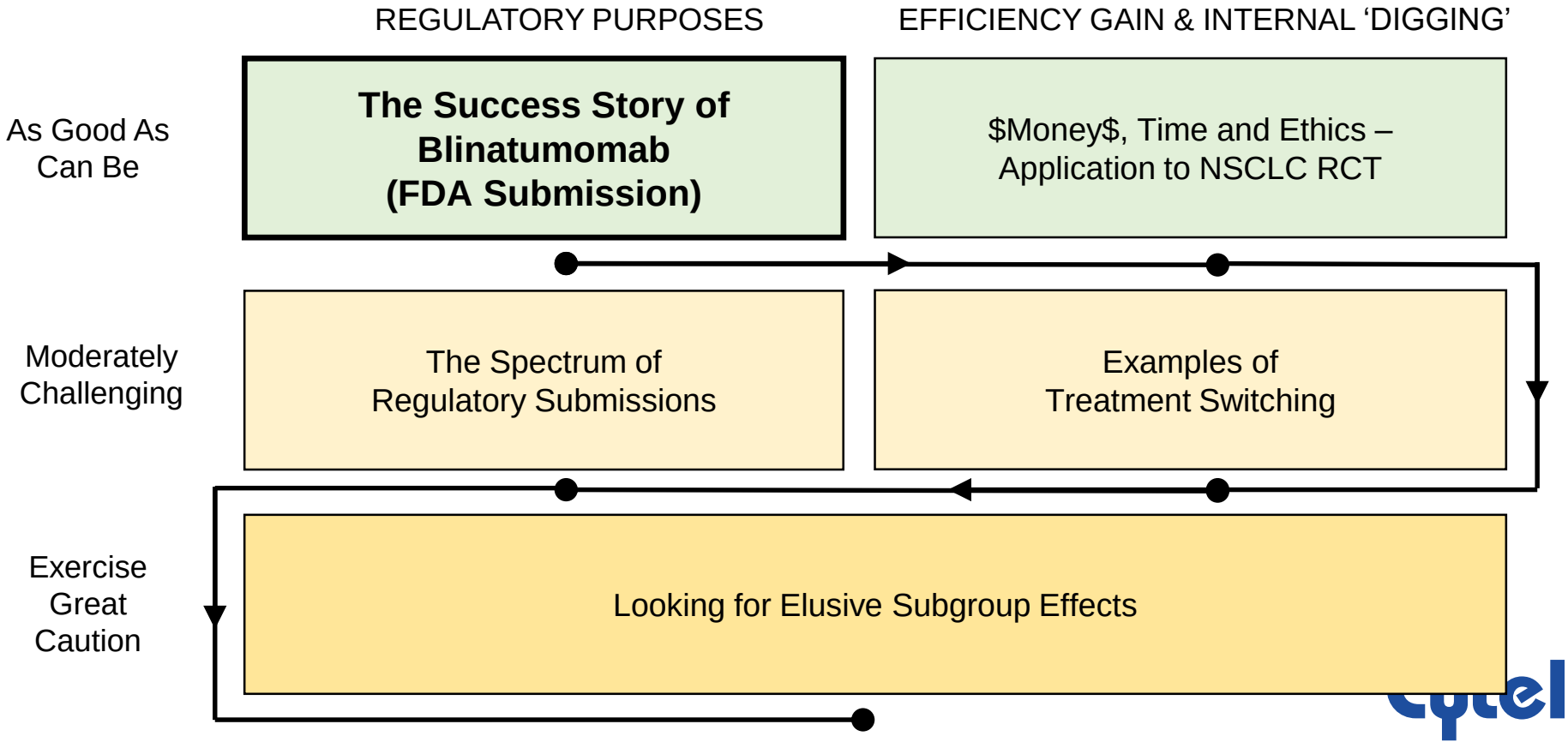

The Success Story of Blinatumomab

OPEN

Citation: Blood Cancer Journal (2016) **6**, e473; doi:10.1038/bcj.2016.84

www.nature.com/bcj

ORIGINAL ARTICLE

Blinatumomab vs historical standard therapy of adult relapsed/ refractory acute lymphoblastic leukemia

N Gökbuget[1], M Kelsh[2], V Chia[2], A Advani[3], R Bassan[4], H Dombret[5], M Doubek[6], AK Fielding[7], S Giebel[8], V Haddad[9], D Hoelzer[1], C Holland[10], N Ifrah[11], A Katz[2], T Maniar[12], G Martinelli[13], M Morgades[14], S O'Brien[15], J-M Ribera[14], JM Rowe[16], A Stein[17], M Topp[18], M Wadleigh[19] and H Kantarjian[15]

We compared outcomes from a single-arm study of blinatumomab in adult patients with B-precursor Ph-negative relapsed/ refractory acute lymphoblastic leukemia (R/R ALL) with a historical data set from Europe and the United States. Estimates of complete remission (CR) and overall survival (OS) were weighted by the frequency distribution of prognostic factors in the blinatumomab trial. Outcomes were also compared between the trial and historical data using propensity score methods. The historical cohort included 694 patients with CR data and 1112 patients with OS data compared with 189 patients with CR and survival data in the blinatumomab trial. The weighted analysis revealed a CR rate of 24% (95% CI: 20–27%) and a median OS of 3.3 months (95% CI: 2.8–3.6) in the historical cohort compared with a CR/CRh rate of 43% (95% CI: 36–50%) and a median OS of 6.1 months (95% CI: 4.2–7.5) in the blinatumomab trial. Propensity score analysis estimated increased odds of CR/CRh (OR = 2.68, 95% CI: 1.67–4.31) and improved OS (HR = 0.536, 95% CI: 0.394–0.730) with blinatumomab. The analysis demonstrates the application of different study designs and statistical methods to compare novel therapies for R/R ALL with historical data.

Blood Cancer Journal (2016) **6**, e473; doi:10.1038/bcj.2016.84; published online 23 September 2016

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

BLA/Serial Number #:	BLA 125557 / 00
Supplement #:	Original Biologics License Application
Drug Name:	Blincyto (blinatumomab) for continuous intravenous infusion
Indication(s):	Treatment of adults with Philadelphia chromosome negative relapsed or refractory B-precursor acute lymphoblastic leukemia
Applicant:	Amgen
Date(s):	Submission date: 19 September 2014
	PDUFA date: 19 May, 2015

- Accelerated FDA approval in 2014
- Ph-negative B-precursor cell relapsed/refractory acute lymphoblastic leukemia
- Single-arm phase II trial (MT103-211; n = 189*)
- Synthetic control arm of clinical trial data from 11 databases in the US and EU (n = 694 for CR and 1112 for OS)
- Estimated the control rate and treatment effect using synthetic control arm

**NOTE: 4 patients who were not within the definition of relapsed/refractory ALL were excluded from the FDA submission*

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Estimation of the Control Rate for Complete Response[1]

Table 2. Stratified and weighted analysis results: comparison of historical data and blinatumomab clinical trial data: CR by strata and weighted to blinatumomab clinical data

Stratum Definition		*Blinatumomab trial (MT103-211)*				*Historical data set*			
Age	*Disease status*	N	*Stratum proportion (%)*	*Number with CR* [a]	*CR/CRh % (95% CI)*	N	*Stratum proportion (%)*	*Number with CR*	*CRsg % (95% CI)*
< 35	Prior alloHSCT[b]	40	21.2	15	38 (23, 54)	48	6.9	14	29 (17, 44)
< 35	In 1st salvage[c]	10	5.3	7	70 (35, 93)	119	17.1	52	44 (35, 53)
< 35	In 2nd or greater salvage[c]	40	21.2	17	43 (27, 59)	150	21.6	27	18 (12, 25)
⩾35	Prior alloHSCT[b]	24	12.7	14	58 (37, 78)	41	5.9	11	27 (14, 43)
⩾35	In 1st salvage[c]	19	10.1	5	26 (9, 51)	187	26.9	57	30 (24, 38)
⩾35	In 2nd or greater salvage[c]	56	29.6	23	41 (28, 55)	149	21.5	25	17 (11, 24)
Combined weighted summary		189	100	81	43 (35, 50)	694	100	186	24 (20, 27)

Note: 186/694 = 27%; estimated 95% confidence intervals using bootstrapping; also conducted sensitivity analyses by time period

[1] Gökbuget N, Kelsh M, Chia V, Advani A, Bassan R, Dombret H, Doubek M, Fielding AK, Giebel S, Haddad V, Hoelzer D. Blinatumomab vs historical standard therapy of adult relapsed/refractory acute lymphoblastic leukemia. Blood cancer journal. 2016;6(9):e473.

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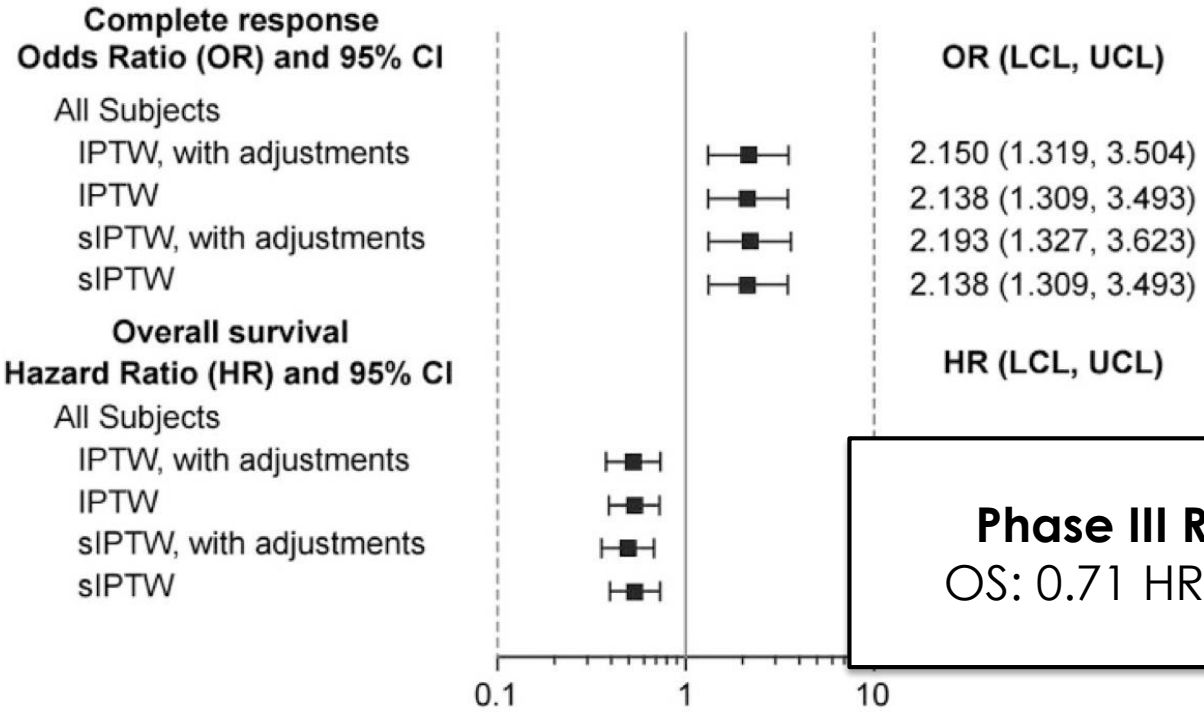
Estimation of treatment effect[1]

Results from IPTW weighted logistic regression and Cox PH models



Phase III RCT (2017)
OS: 0.71 HR (0.55-0.93)

[1] Gökbuget N, Kelsh M, Chia V, Advani A, Bassan R, Dombret H, Doubek M, Fielding AK, Giebel S, Haddad V, Hoelzer D. Blinatumomab vs historical standard therapy of adult relapsed/refractory acute lymphoblastic leukemia. Blood cancer journal. 2016;6(9):e473.

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Summary of Blinatumomab Case Study

- Synthetic control arms can lead to regulatory approval without a head-to-head comparison in a phase III trial

- Success of Blinatumomab can be attributable to the:
    1) Appropriateness of the indication
    2) Proper identification of external control
    3) Robustness of the statistical analyses

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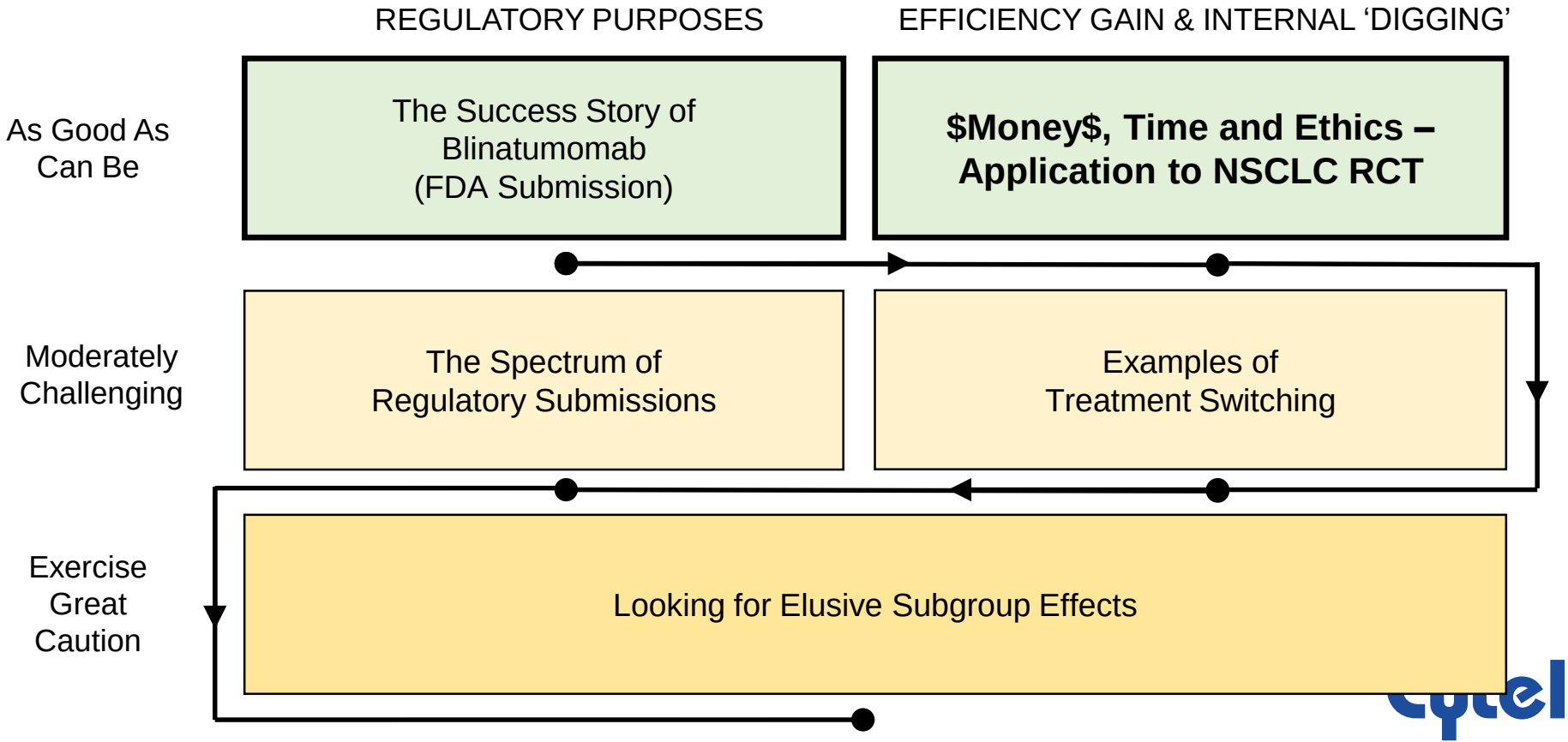
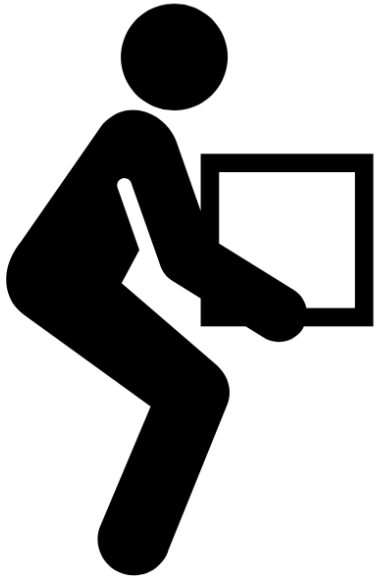
• Non-Bullet Point Outline



Dynamic borrowing



- Information from one or more external data sources are **borrowed** to augment the control arm and allow for unequal randomization (e.g. 3:1)
- Heterogeneity between the control arm and the external data are assessed
- The external data are **dynamically** down-weighted proportional to the degree of similarity between the external and control arms

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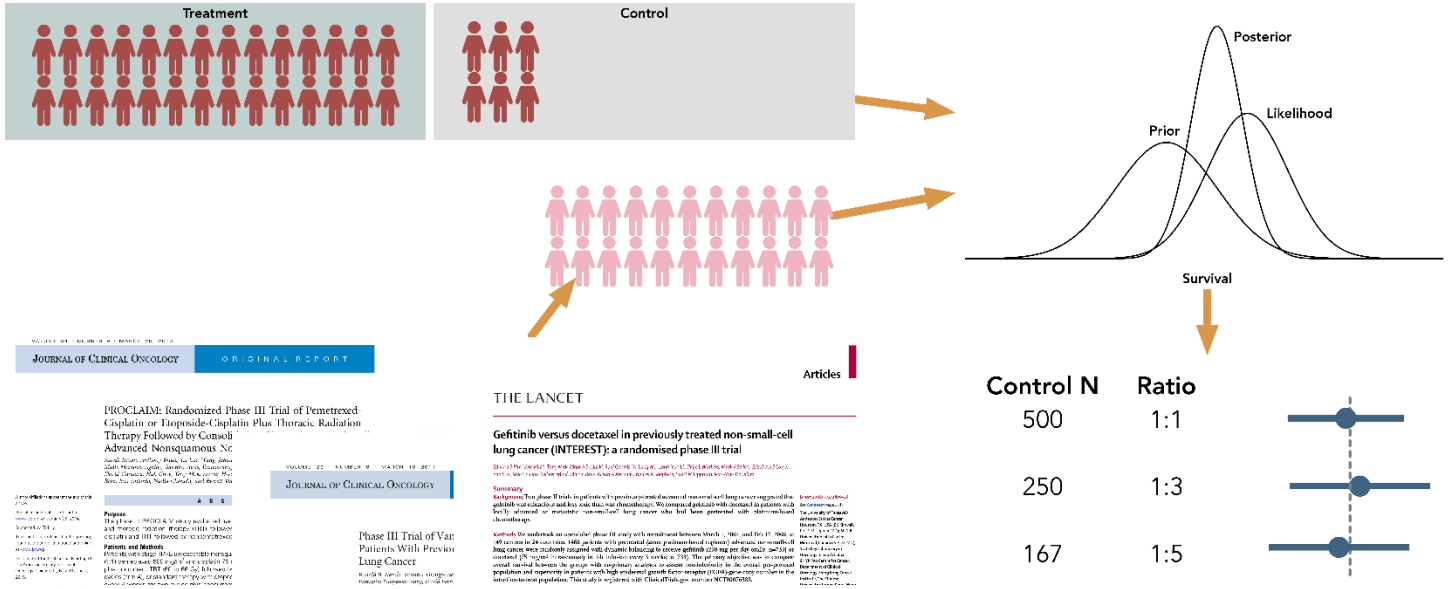
Estimation via dynamic Bayesian borrowing



- Bayesian methods can dynamically borrow from historical data sources using informative priors
- Viele (2014) and Wadsworth (2019) provide an overview of statistical methods[1,2]

[1] Viele K, Berry S, Neuenschwander B, Amzal B, Chen F, Enas N, Hobbs B, Ibrahim JG, Kinnersley N, Lindborg S, Micallef S. Use of historical control data for assessing treatment effects in clinical trials. Pharmaceutical statistics. 2014 Jan;13(1):41-54. [2] Wadsworth I, Hampson LV, Jaki T. Extrapolation of efficacy and other data to support the development of new medicines for children: a systematic review of methods. Statistical methods in medical research. 2018 Feb;27(2):398-413.

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Case Study[1]

Characteristic	INTEREST	ZODIAC	PROCLAIM	Study 57
Overall sample size (*n*)	1433	1391	598	1240
Control group median overall survival, months (Q1, Q3)	8 (4, 14)	10 (4, 13)	25 (10, 35)	8 (4, 12)
Stage III, (%)	38	15	100	17
Stage IV, (%)	53	85	0	83
Average age, (years)	61	59	59	61
Adenocarcinoma histology, (%)	54	60	75	60
Two or more prior chemotherapy regimens, (%)	16	0	0	35
Radiotherapy sequence, dose, (control arm)	None	None	60-66Gy, Concurrent	None

- We used IPD from four second line non-small cell lung cancer trials for patients with stage III/IV disease.
- Used the INTEREST trial as the 'anchor' trial and simulated its performance with fewer patients randomized to control, but ***dynamically borrowing*** from the three other trials' control groups

Dron L, Golchi S, Hsu G, Thorlund K. Minimizing control group allocation in randomized trials using dynamic borrowing of external control data–An application to second line therapy for non-small cell lung cancer. Contemporary clinical trials communications. 2019 Dec 1;16:100446.

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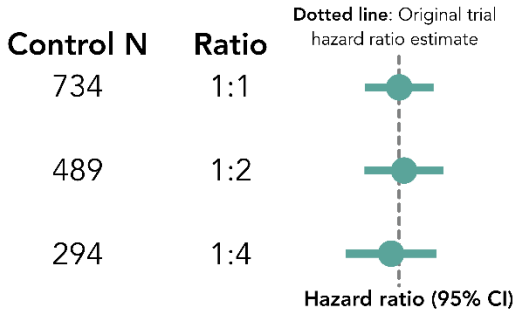
Case Study[1]



- In the original trial (INTEREST) 734 patients were recruited to control
- With a 1:1, a 1:2 or a 1:4 ratio of control patients to borrowed controls, we demonstrate a relatively minor change in precision
- Testing various scenarios showed that the control arm can be reduced by up 60% without jeopardizing the validity of statistical inferences
- The findings also applied where external control data was heterogeneous, but not inconsistent with the concurrent control

Dron L, Golchi S, Hsu G, Thorlund K. Minimizing control group allocation in randomized trials using dynamic borrowing of external control data–An application to second line therapy for non-small cell lung cancer. Contemporary clinical trials communications. 2019 Dec 1;16:100446.

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The FDA recognizes the role of dynamic borrowing[1,2]

"This document provides guidance to sponsors and applicants on interacting with the FDA on complex innovative trial design (CID) proposals for drugs or biological products. FDA is issuing this guidance to satisfy, in part, a mandate under section 3021 of the 21st Century Cures Act […] Some examples of trial designs that might be considered novel or CID are those that ***formally borrow*** *external or historical information or borrow control arm data from previous studies* ***to expand upon concurrent controls.***"[2]

[1] 2019 FDA guidance for Rare Diseases: Natural History Studies for Drug Development.
[2] 2019 FDA guidance for Interacting with the FDA on Complex Innovative Clinical Trial Designs for Drugs and Biological Products

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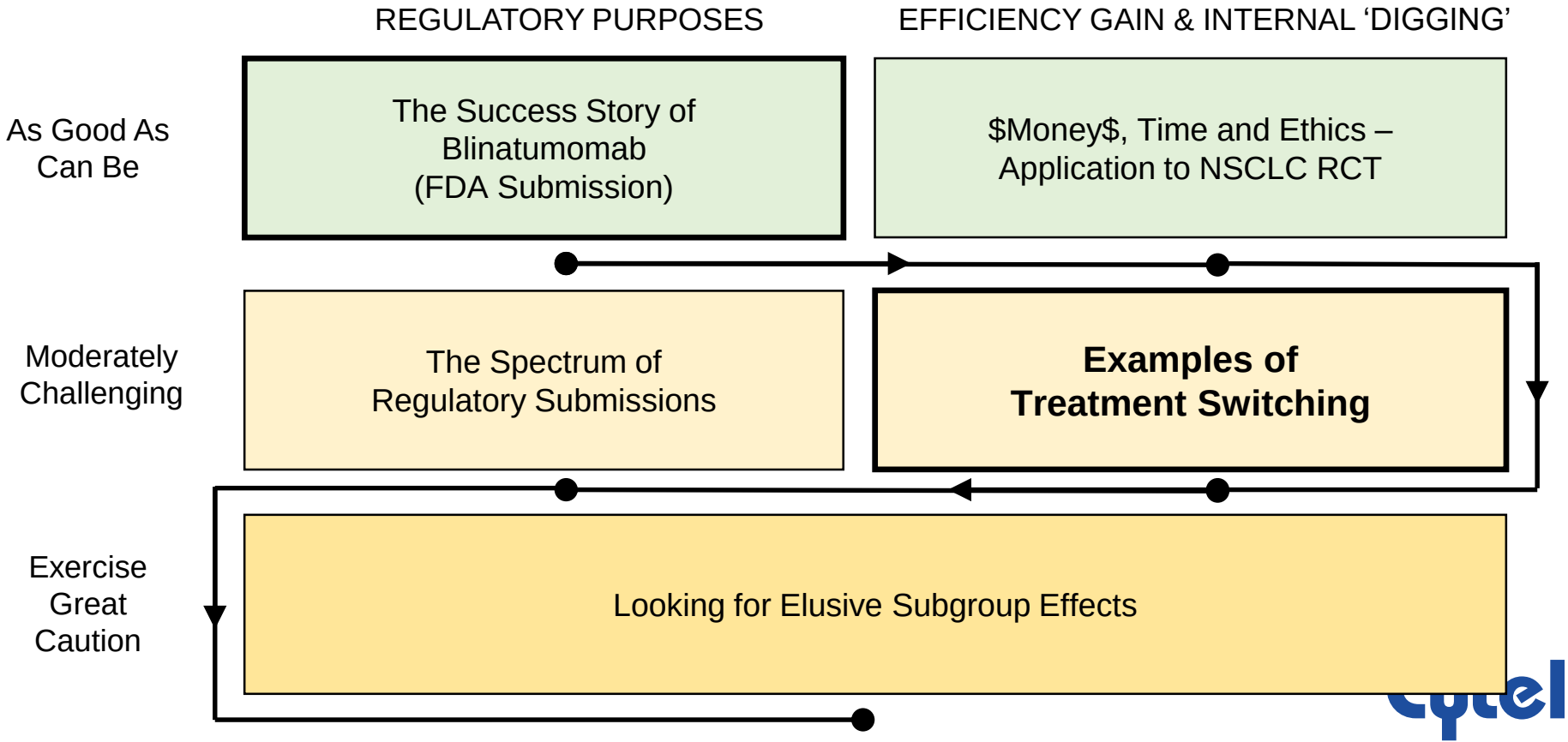
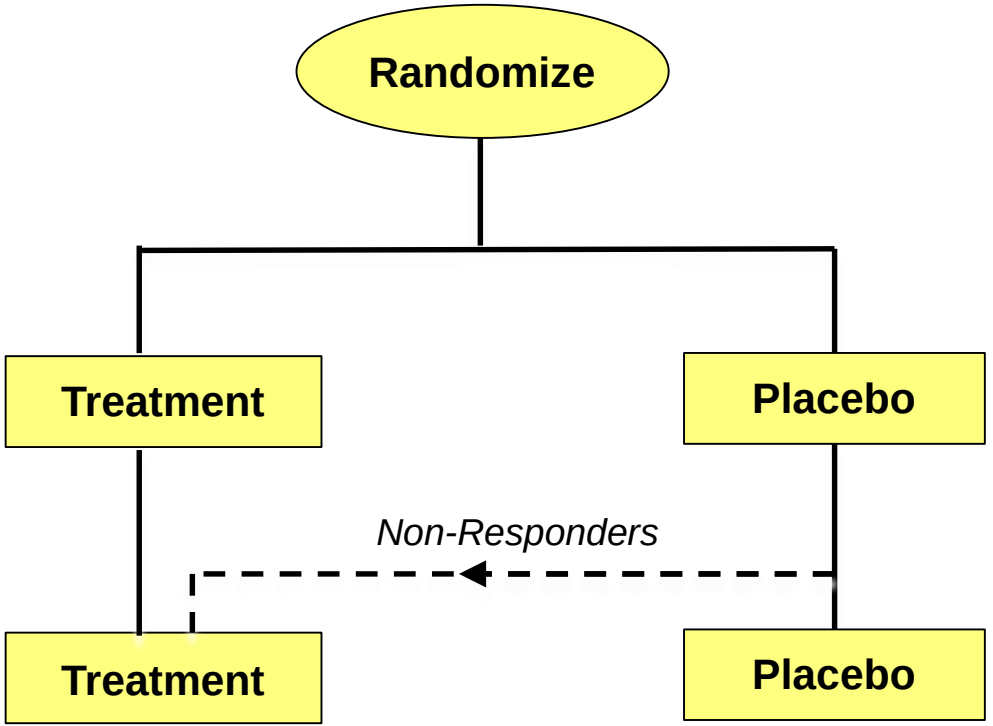
• Non-Bullet Point Outline



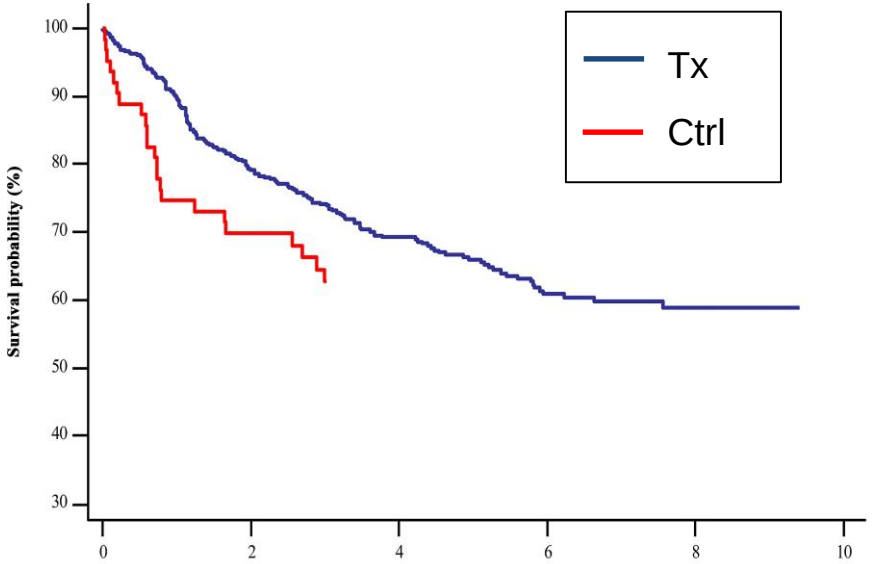
When ethics impede data utility in placebo cross-over designs

- Placebo cross-over can result in substantial reductions in 'true' placebo sample size or duration
- Common in:
  - Auto-immune diseases
  - Cancers with poor prognosis
  - Chronic diseases with 1st, 2nd, 3rd, … lines of Tx

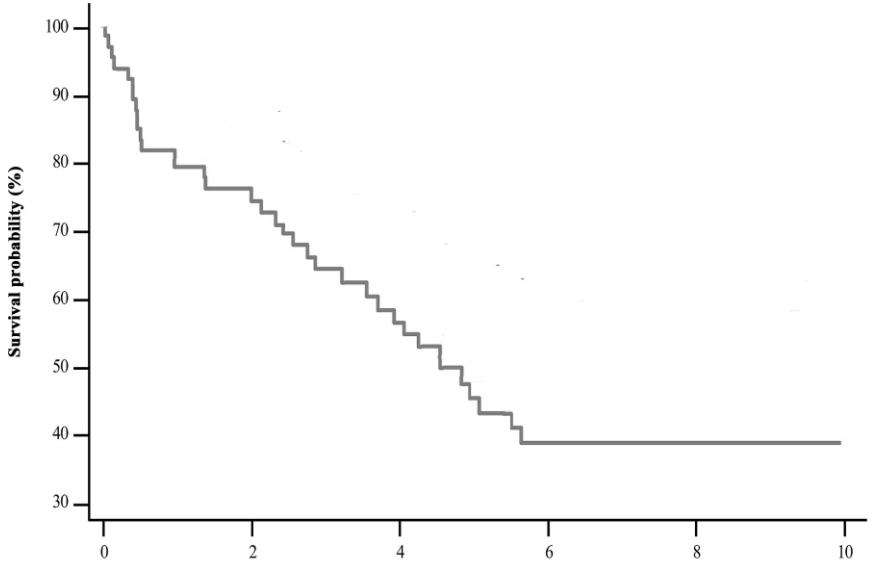


When ethics impede data utility in placebo cross-over designs

Trial with Cross-Over at 3 Months



Historical Control Cohort



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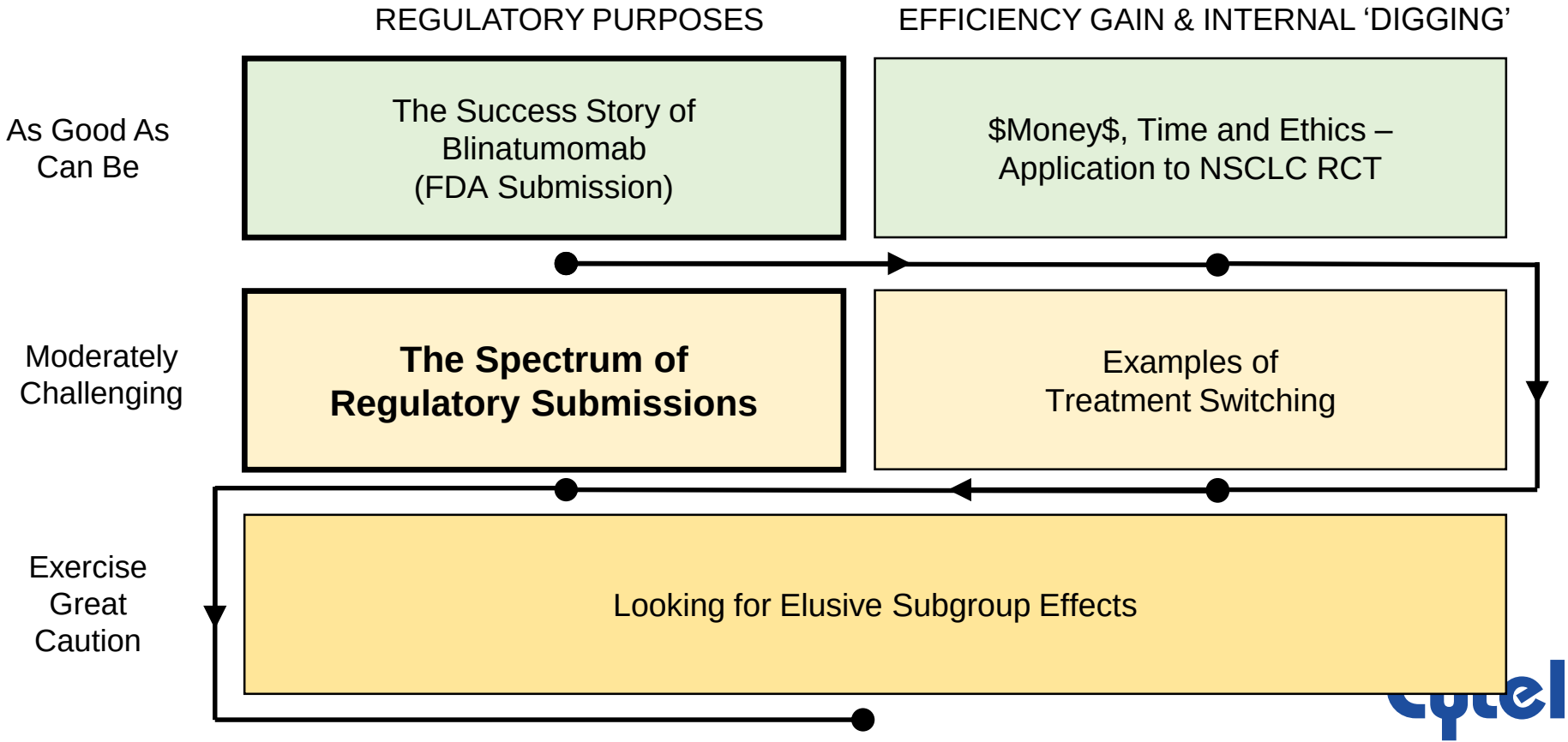

Regulatory landscape – an overview

Received: 13 March 2019 | Revised: 17 September 2019 | Accepted: 11 November 2019
DOI: 10.1002/pds.4932

REVIEW

WILEY

Trial designs using real-world data: The changing landscape of the regulatory approval process

Elodie Baumfeld Andre[1] | Robert Reynolds[1,2] | Patrick Caubel[1] | Laurent Azoulay[3,4] | Nancy A. Dreyer[5,6]

TABLE 2 Examples of recent regulator-supported initiatives that drive forward the application of RWE

	Details of the Initiative
Guidance to submit documents using real-world data and real world evidence to FDA for drugs and biologics (2019)[24]	This guidance is intended to encourage sponsors and applicants who are using RWD to generate RWE as part of a regulatory submission to FDA to provide information on their use of RWE in a simple, uniform format.
HMA/EMA Joint Task Force on Big Data (2019)[25]	This document provides recommendations for a path towards understanding the acceptability of RWE from "Big data" sources to support regulatory evaluation and monitoring.
Framework for FDA: Real-world evidence program (2018)[8]	The FDA published a framework to help evaluate the potential use of RWE to support new indications for drugs already approved or to satisfy post-approval study requirements. This framework demonstrates a commitment to transforming the drug development cycle.
Guidance on the use of Electronic Health Records (FDA) (2018)[26]	The focus of this guidance is on data integrity. It emphasizes the need to cite the "data originator" and preserve the audit trail. It also reinforces that RWE may be used to inform approval of new indications for approved drugs and to satisfy post-approval study requirements.

- Baumfeld Andre et al. 2019 is a high quality of review of trial designs utilizing real-world data as part of their submissions.
- They provide examples of 22 submissions to the EMA and FDA which utilized real-world evidence as part of their submission process for approvals (either accelerated or full).
- They identified most applications were for either rare metabolic disease or rare oncology applications

DOI: 10.1002/pds.4932

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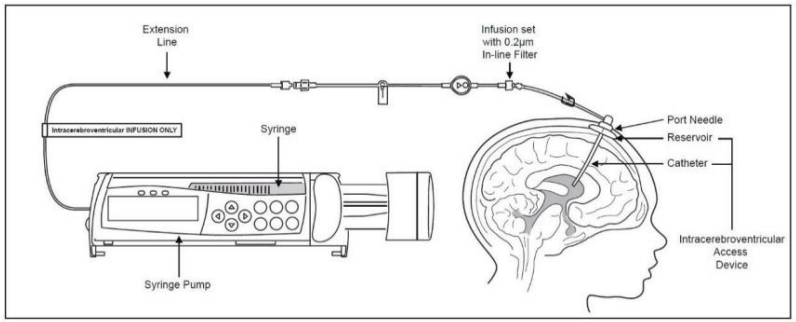
Regulatory landscape – complexity ≠ success



An illustration of the Brineura intracerebroventricular infusion process.

- Cerolipinase alfa (Brineura) is a treatment for Batten disease - a rare inherited nervous system disorder.
- Owing to the disease rarity and the associated treatment administration, a small, single-arm trial of 22 patients was conducted.
- Efficacy data was compared (using a 1:1 matching algorithm) to a well-defined historical natural history cohort of 42 patients.
- FDA/EMA approval was granted on the basis of this comparison.

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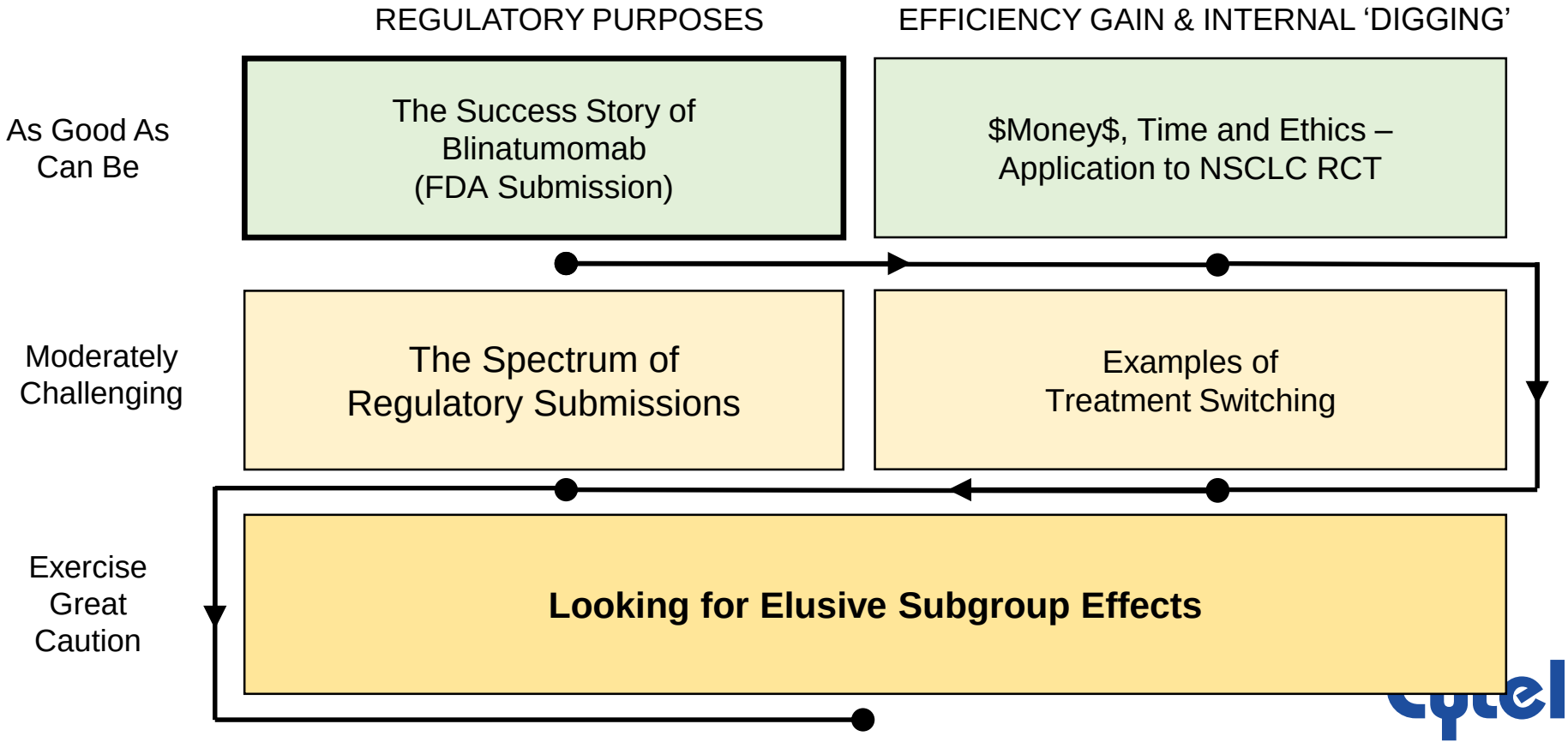
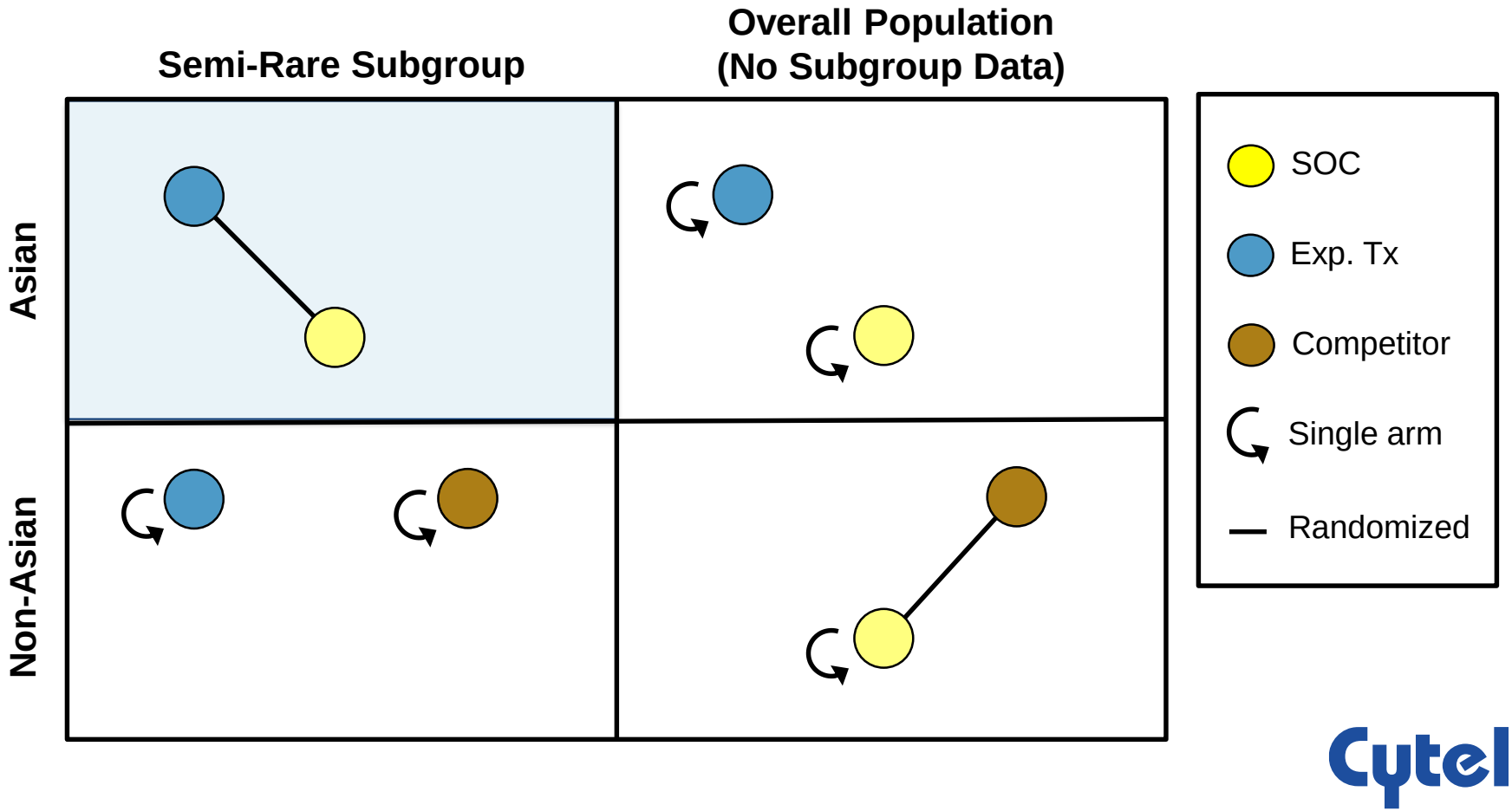
• Non-Bullet Point Outline



When things get a bit too messy



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So what have we learned?

Data source(s)	Well-Designed RCT(s) Comparable Covariate Data	Prospective Cohorts/ Prospective Registries Limited Covariates	Limited Sample Size Limited Covariate Data High Missingness
Similarity of datasets	Similarity of Geographic region(s) Demographics Disease and Outcome Definitions	Adequate Sample Size for Covariate Matching Manageable Differences in Disease and Outcome	Substantial Differences in Distribution of Covariates, or Disease and Outcome Definitions
Methods of Analysis	Use of Concurrent Control Data, Adequate Sample Size Robust Adjustment	No Concurrent Control Data. Mild Dissimilarities Acceptable Robustness	No Concurrent Control Data Substantial Dissimilarities High Sensitivity to Methods
Relevance and reliability	High Patient and Outcome Similarity No Apparent Biases Adequate Sample Size Adequate Number of Covariates	Adjustments not Representative of Population. Biases on External Control Outcomes.	Data Set not Representative of Target Population Adjustments not Feasible

Thank You!

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