

Cost Benefit Analysis of using CDISC Standards in Trial Set-up

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ABSTRACT

This presentation originated from the desire of the management of a midsize pharma company to get more insights in the value of implementing a metadata repository with the goal of implementing standards from the start. Assuming that it is possible to achieve 100% standardization, how much effort would still be required to set up a trial? And what is the effort to achieve 100% standardization?

The analysis was completed using an anonymized real life model of an outsourced phase III trial in a new indication. To allow full comparison, cost of time, effort and quality were quantified and standardized to effort (manhours).

The analysis shows that while there is a significant impact in setting up a trial from no standardization to some level of standardization, the time gain for setting up a trial from high level of standardization to a fully standardized trial rapidly diminishes. On the other hand the cost of Quality Control is significantly reduced in a fully standardized trial over one that is highly standardized.

This presentation aims to show a clear picture of both the cost and the benefits for implementation of standards, including thoughts on how to define a model that is right for your organization.

INTRODUCTION

This analysis includes a retrospective and prospective analysis based on real data as our industry has evolved through different levels of standardization and technology implementation. It provides insights into why we should see huge benefits in standardization, but often may not see the same results when putting the effort into practice. It concludes with recommendations on deciding what type of standardization is right for your organization and the long term benefits beyond the return on Investment.

PART I: VALUE OF STANDARDS

METHODOLOGY

The scope of the analysis includes the activities related from the design of the study (protocol or protocol outline) until creation of SDTM and define.xml. In the calculations "Effort" includes the study design discussions, EDC design and build, integration of electronic data streams, User Acceptance Testing, creation of Documentation and mapping or conversion to SDTM, including creation of define.xml, where data managers, data base designers and/or programmers are involved.

The analysis compares 3 levels of standardization (50%, 80% and full standardization) against no standardization. To evaluate the true cost of trial set-up, variable costs not associated with trial set-up effort (such as EDC hosting) were excluded, and hourly rates across cost proposals were harmonized to exclude regional variability. Effort calculators were built to model the cost of a trial. To compare trial set-up effort of the different levels of standardization, the following parameters were fixed:

- # subjects
- # sites
- Trial Duration

For each level of standardization the effort calculator was run to see the effect on complex trials (multiple or complex efficacy endpoints, phase II/III trials in complex disease areas) and on standard trials (phase I trials, non-interventional or well-defined endpoints). These results were plotted in a graph.

OBSERVATIONS

Three main conclusions were drawn from the data

1. ***Any level of standardization will result in a reduction of set-up effort and the impact of standardization is higher for complex trials (fig. 1).***

This should not be surprising. Once standards are defined, the effort does not have to be repeated, provided there is a discipline within the team to adhere to standards.

As the absolute cost of a complex trial is assumed to be higher than the absolute cost of a standard trial, the opportunity to achieve a benefit is higher in complex trials than in standard trials. Often more people are involved and simply not needing to have a discussion about something in a large team meeting creates a bigger benefit than not having the discussion in a small team (calculating manhours).

Impact of standardization on trial set-up effort

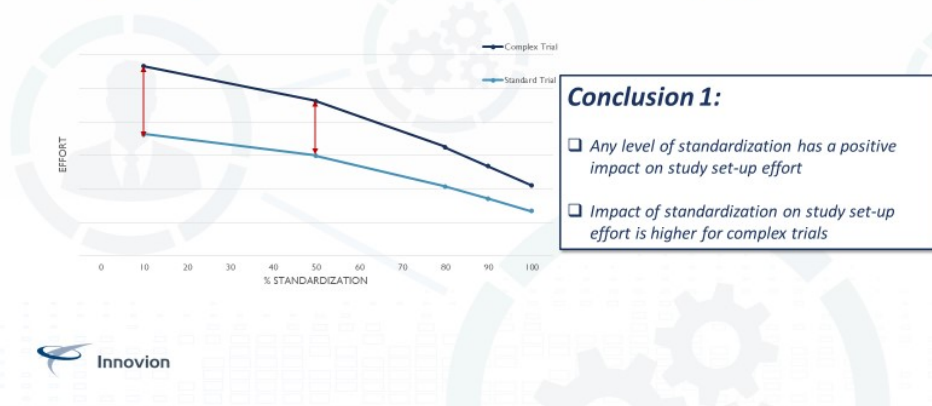


Figure 1

2. The more you invest in standards, the bigger the impact (fig. 2)

So while a basic level of standardization will already give immediate benefits, the reality is that when developing standards, most teams will start with defining “the obvious”. The more detailed the standards development becomes, the more likely that complex issues, such as endpoint definitions are defined. While the immediate gain means that fewer topics are rediscussed, one can also introduce efficiencies by changing training and validation procedures (validate once, use many times). Lastly the QC effort is significantly reduced and may even be automated if you can verify deliverables against pre-defined specifications.

Impact of standardization on trial set-up effort

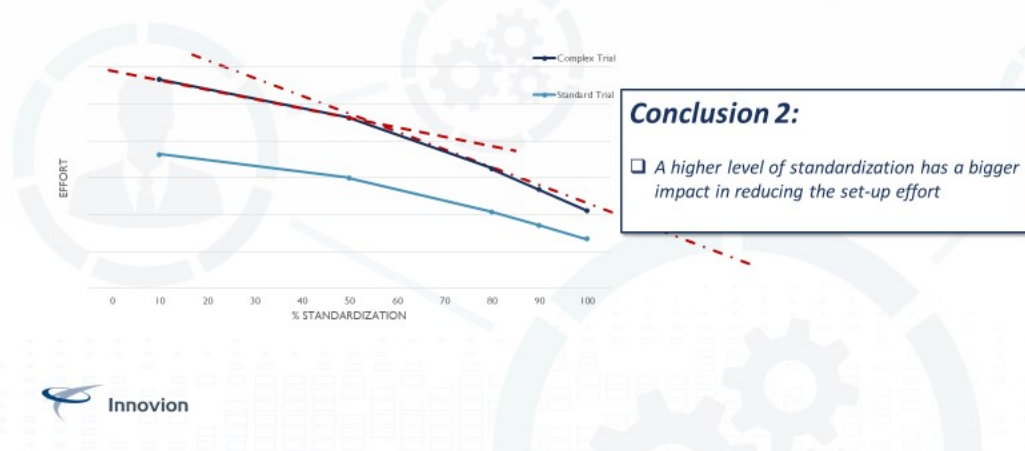


Figure 2

3. There is a finite benefit to be gained from standardization (fig. 3)

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This part is often overlooked and is the reason why statements on the extreme benefits of standards are challenged. The purpose of doing trials is to gather insights through data collected, therefore, as long as a company wants to learn, it will have to introduce new science, new hypotheses. This implies that a library of standards is never static. Using standards to set-up trials will bring the discussion forward, but the discussion still needs to take place. There seems to be a “golden rule” in our industry that there is a 12 week period between final protocols and first subject recruited, and unfortunately this is where we lose momentum. Most humans work best with a deadline

Impact of standardization on trial set-up effort

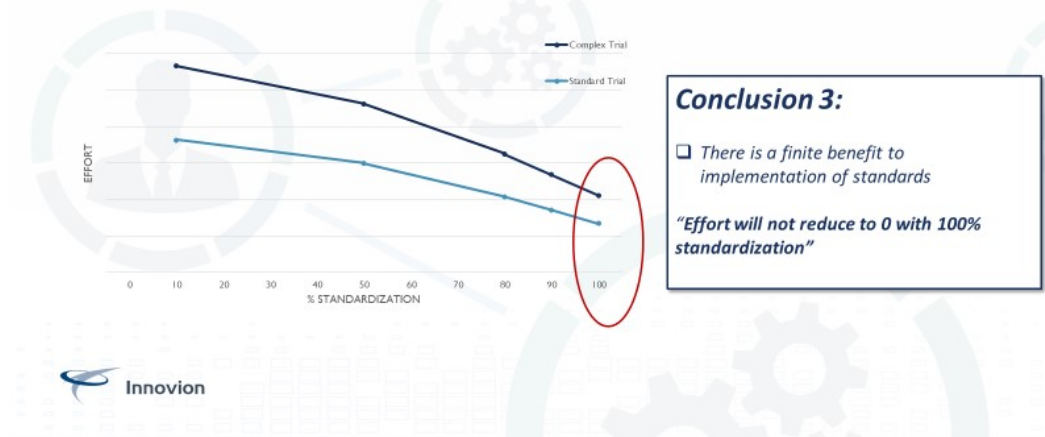


Figure 3

PART II: DEFINING THE RETURN ON INVESTMENT

Definitions

Basic Standardization: A company that is new to implementing standards, will usually opt to implement the domains well described in the CDISC SDTM Implementation Guide first. We would recommend creating visualizations, add the associated controlled terminology and CDASH/SDTM annotations and define conventions, such as reference dates and basic computational algorithms. This level of standardization will use material already available and does not require any significant technology investment.

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AE	ADVERSE EVENTS	DCM ID: AE_GL_001
STUDYID	Study	[Free text]
SITEID	Site	[Free text]
SUBJID	Subject	[Free text]
Adverse Events		
[Not Submitted]	AEYN	Were any adverse events experienced?
AESPID	AESPID	AE number
AETERM	AETERM	What is the adverse event term?
AESTDTC	AESTDAT	Start Date
	AESTTIM	Start Time
AEENDTC	AEENDAT	End Date
	AEENTIM	End Time
If Yes, AEENRPT ONGOING	AEONGO	Is the adverse event still ongoing?
AESER	AESER	Severity
		Is the adverse event serious?
		If Yes:
AERFID	AERFID	SAE Number
AESCONG	AESCONG	Congenital Anomaly
AESDISAB	AESDISAB	Significant Disability
AESDTH	AESDTH	Death
AESHOSP	AESHOSP	Hospitalization
AESLIFE	AESLIFE	Life Threatening
AESMIE	AESMIE	Other Medically Important Event
		[Radiobutton (Not related; Unlikely Related; Possibly Related; Probably Related)]
AEREL	AEREL	Relationship to Study Treatment
		[Radiobutton (Dose Not Changed; Drug Withdrawn; Dose Reduced)]
AEACN	AEACN	Action taken with Study Treatment

SDTM

CDASH

CRF questions

eDC build instructions

Controlled terminology

Figure 1: snapshot of a visualization of basic standardization

Advanced Standardization: The next level of the standardization effort will include the definition of regularly recurring disease area specific assessments and endpoints and the associated metadata. The main goals and advantages of an advanced standardization are the re-use of library templates across studies and unambiguous communication between sponsors and vendors. Sponsors will be able to define study expectations in a common human and machine-readable format. In view of submissions and exploratory analysis, the consistency across trials will facilitate data pooling.

ADVERSE EVENTS			DCM ID: AE_GL_001													
STUDYID	STUDYID	Study	[Free text]	[Preprinted]												
SITEID	SITEID	Site	[Free text]	[Preprinted]												
SUBID	SUBID	Subject	[Free text]	[Preprinted]												
Adverse Events	Dataset	Description	Class	Structure	Purpose	Key Variables	Repeating	Reference Data								
[Not Submitted]	AE	Adverse Events	EVENTS	One record per adverse event per subject	Tabulation	STUDYID,USUBJID,AECAT,AEDECOD,AESTDTC	Yes	No								
AE#	Dataset	Variable	Label	Data Type	Length	Digits	Format	Mandatory	Code list	Origin	Pages	Method	Predecessor	Role	Comment	Core
AE#	AE	STUDYID	Study Identifier	text	12			Yes		Protocol				Identifier		Req
AE#	AE	DOMAIN	Domain Abbreviation	text	2			Yes	AE.DOMAIN	Assigned				Identifier		Req
AE#	AE	USUBJID	Unique Subject Identifier	text	18			Yes		Derived			USUBJID	Identifier		Req
AE#	AE	AESEQ	Sequence Number	integer	8			Yes		Derived			SEQ	Identifier		Req
AE#	AE	AEGRPID	Group ID	text	20			No		Derived			AEGRPID	Identifier		Perm
AE#	AE	AERFPID	Reference ID	text	20			No		CRF				Identifier		Perm
AE#	AE	AESPD	Sponsor-Defined Identifier	text	20			No		CRF				Identifier		Perm
AE#	AE	AETERM	Reported Term for the Adverse Event	text	200			Yes		CRF				Topic		Req
AE#	AE	AEMODIFY	Modified Reported Term	text	200			No		Assigned				Synonym Qualifier		Perm
AE#	AE	AE1LT	1st Listed Local Term	text	200			No	MedDRA	Assigned				Variable Qualifier		Exp
ID	Name	NCI	NCI Code list	Data Type	Order	Term	NCI	NCI Term Code	Decoded Value	Extensibi						
ACN	Action Taken with Study Treatment	C66767	text	DOSE INCREASED	C49503	Dose Increased	N	Exp								
ACN	Action Taken with Study Treatment	C66767	text	DOSE NOT CHANGED	C49504	Dose Not Changed	N	Exp								
ACN	Action Taken with Study Treatment	C66767	text	DOSE REDUCED	C49505	Dose Reduced	N	Exp								
ACN	Action Taken with Study Treatment	C66767	text	DRUG INTERRUPTED	C49501	Drug Interrupted	N	Exp								
ACN	Action Taken with Study Treatment	C66767	text	DRUG WITHDRAWN	C49502	Drug Withdrawn	N	Perm								
ACN	Action Taken with Study Treatment	C66767	text	NOT APPLICABLE	C48660	Not Applicable	N	Perm								
ACN	Action Taken with Study Treatment	C66767	text	UNKNOWN	C17998	Unknown	N	Exp								
AE#	AE	AEOSCO	Body System or Organ Class Code	integer	8	No	MedDRA	Assigned	Variable Qualifier	Exp						
AE#	AE	AEOSC	Primary System Organ Class	text	200	No	MedDRA	Assigned	Variable Qualifier	Exp						
AE#	AE	AEOSCCD	Primary System Organ Class Code	integer	8	No	MedDRA	Assigned	Variable Qualifier	Exp						
AE#	AE	AELOC	Location of Event	text	200	No	LOC	CRF	Record Qualifier	Perm						
AE#	AE	AESEV	Severity/Intensity	text	20	No	AESEV	CRF	Record Qualifier	Perm						
AE#	AE	AESER	Serious Event	text	1	No	NY_YN	CRF	Record Qualifier	Exp						
AE#	AE	AEACH	Action Taken with Study Treatment	text	40	No	ACH	CRF	Record Qualifier	Perm						
AE#	AE	AEACNTH	Other Action Taken	text	20	No	CRF	CRF	Record Qualifier	Perm						
AE#	AE	AEREL	Causality	text	20	No	REL	CRF	Record Qualifier	Exp						
AE#	AE	AERELNG	Relationship to Non-Study Treatment	text	40	No	CRF	CRF	Record Qualifier	Perm						

Figure 2: snapshot of advanced standardization

Full Standardization: The goal of this level of standardization is to provide full [data specifications](#) from data capture through storage and analysis (the latter not in scope of this article). While theoretically it would be possible to achieve this through common tools, such as excel, in practice it does require the investment of a metadata repository (MDR) to develop and maintain standards. Unless you have a dedicated study specifications team that fully understands the construct of an MDR, you would also need a user interface to allow study specific selection of data collection forms and the associated metadata.

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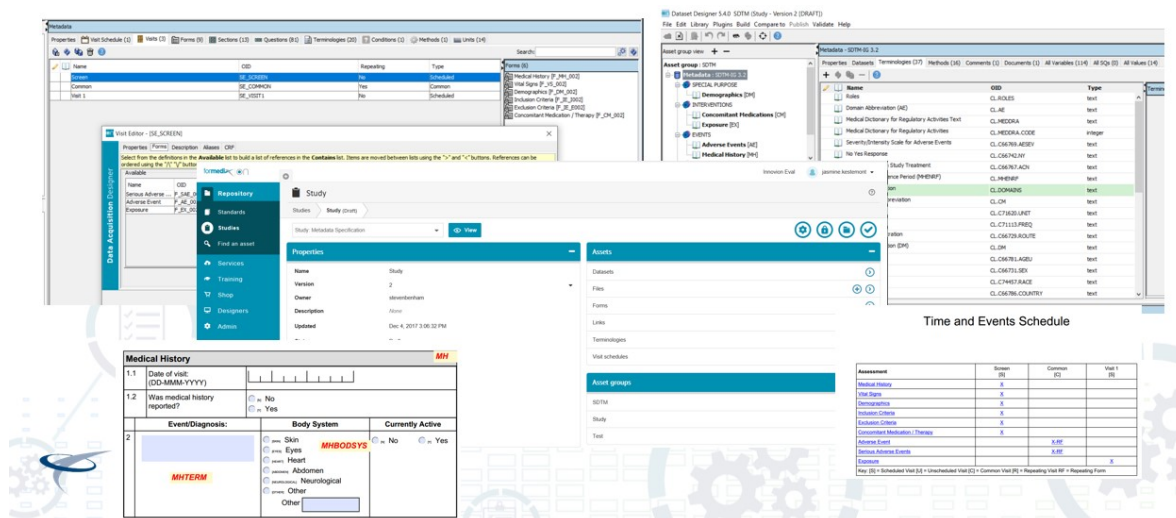


Figure 3: snapshots of a metadata repository

CALCULATING THE BREAK-EVEN POINT

Any level of standardization requires an upfront effort. In this section we will compare the effort of the investment and the gain against the same trials without standardization. The following parameters were considered to calculate the effort:

- **developing standards**
- **governance and maintenance of standards**
- **technology investment**
- **process change and implementation**
- **training**

Benefits of standardization include:

- **communication**
- **quality control, including user acceptance testing**
- **oversight**

1. BASIC STANDARDIZATION VS NO STANDARDIZATION

Basic standardization requires a relatively small upfront investment, common tools such as MS Word will suffice. As it primarily focuses on the domains that are well-defined and thus stable, maintenance of the standards is limited. The largest gain in this process is facilitated communication and a reduction in review effort, but there is limited opportunity to automate any parts of the process.

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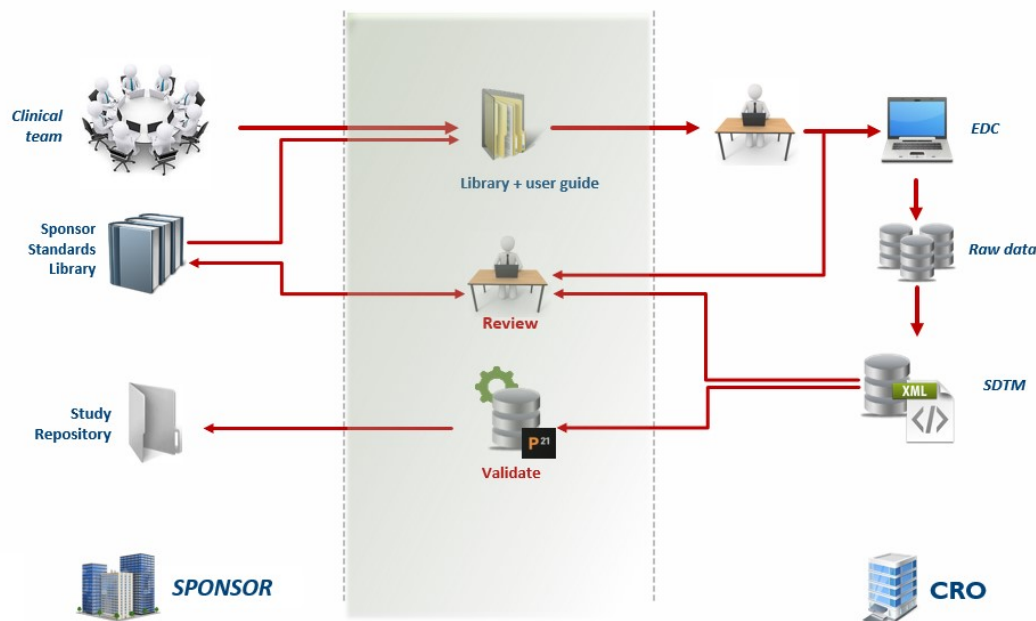


Figure 4: oversight and quality control of an outsourced trial with basic standardization

Nevertheless, we do see a recurring benefit of any level of standardization, and this effort can easily be completed by anyone, new or experienced in the development of standards. When comparing the effort and investment to set up a trial with basic standardization vs no standardization, one can see that, despite the upfront investment, the total budget for setting up 5 trials is cheaper with basic standardization than without standardization.

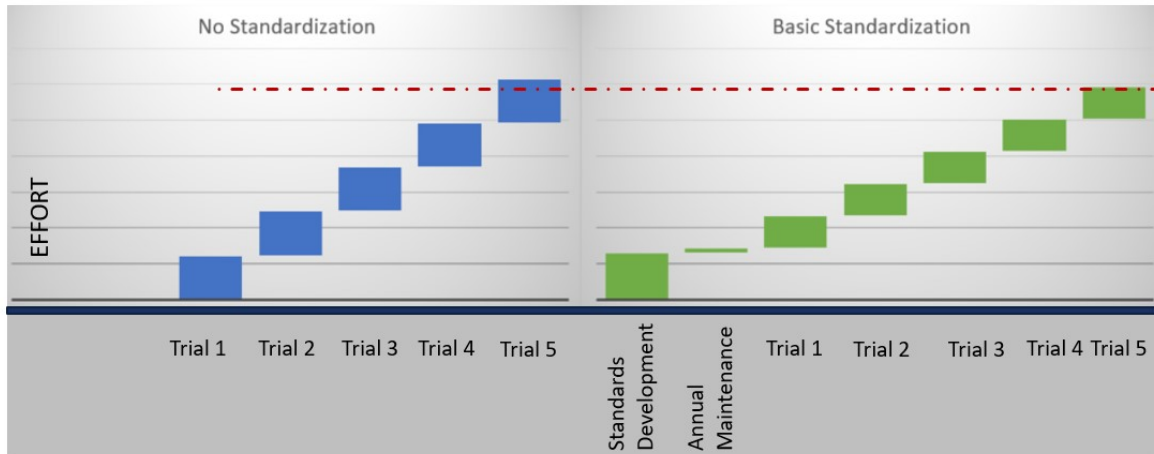


Figure 5: break-even point of basic standardization vs no standardization

2. ADVANCED STANDARDIZATION VS NO STANDARDIZATION

Building advanced standards, looking at the needs of your (or your Sponsor's) trials will require a higher investment in skillsets, training and possibly process updates, on the other hand, the per trial benefit is larger. The need to invest in technology is limited (something as basic as MS Excel will do), provided the team is disciplined and adheres to the standards agreed upon.

Other than providing expectations to your partner which facilitates communication, there are 2 major advantages in set-up. Firstly, it is acceptable to perform user acceptance testing at standards level. For the forms UAT'ed, it is not required to repeat this effort at trial level, provided there is no change to the form. Secondly, it is possible to compare what was provided to the CRO and what has been received in a semi-automated way, thus reducing your quality control efforts and overall oversight.

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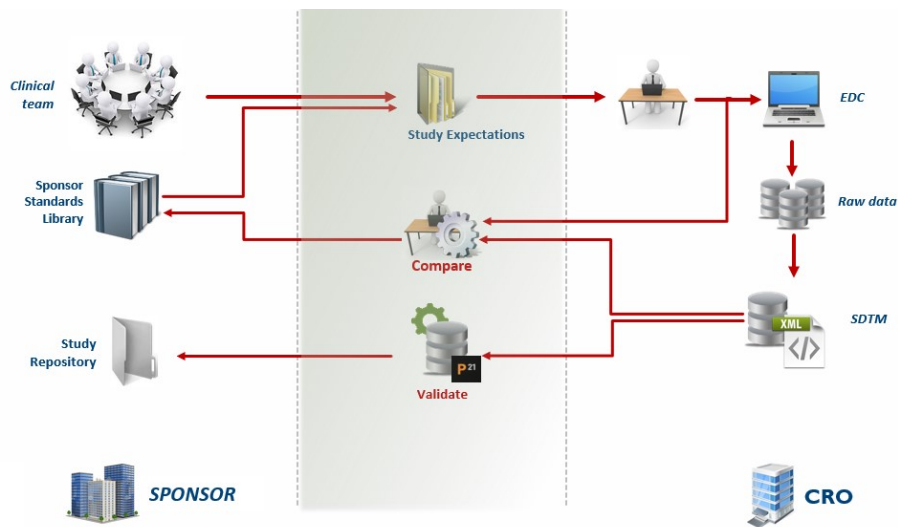


Figure 6: oversight and quality control of an outsourced trial with advanced standardization

This translates to an overall larger effort in the definition of standards, but reduced effort in the per trial set-up. While the initial effort is larger, because of the gain per trial set-up, we again see that the overall budget for setting up 5 trials with advanced standardization is lower than setting up 5 trials without standardization.

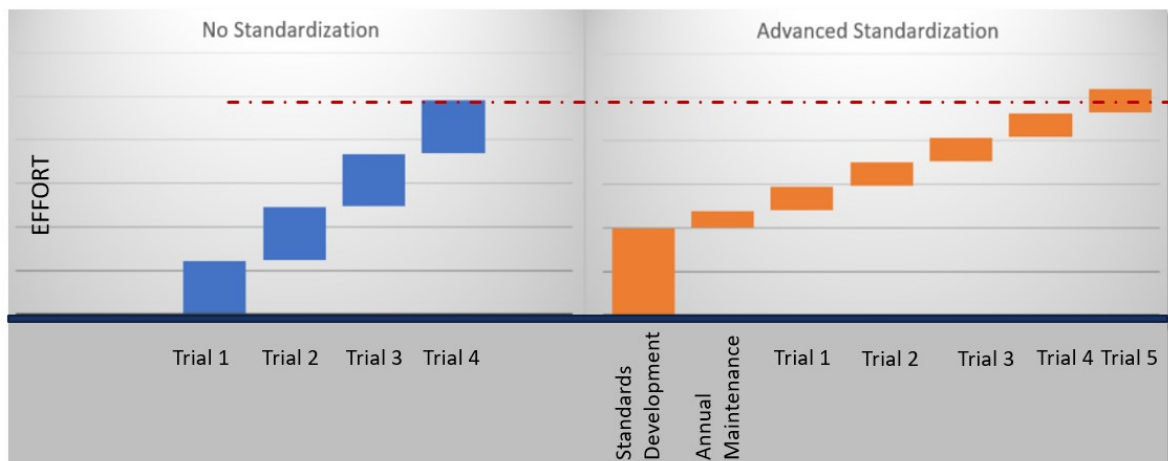


Figure 7: break-even point of advanced standardization vs no standardization

3. FULL STANDARDIZATION VS NO STANDARDIZATION

Finally, we evaluated the effort of full standardization, where the sponsor will provide exact specifications for the trial and will clearly define what to expect back from the CRO. To be able to do this, the sponsor will need to invest in technology (MDR and automation), process updates, monitoring and training to facilitate this. There are multiple technology partners with varying capabilities and associated costs. The below business case was developed using Formedix.

In the calculation, we collated all Standards Development efforts into 1 bucket (standards development), regardless of whether this was done for an individual trial. In practice our experience has been that the effort is concentrated in the first 2 trials and from the 3rd trial onwards there is a significant return on investment. This is because you can build most of your standards based on experience, but the details of trial specific components will only be built as the protocol becomes available. This effort would not go away in any of the other models, but in this model, the responsibility lies with the sponsor or their designated standards development partner. Important to note in this model is that the entire effort of trial set-up is front-loaded, possibly even before first engagement with the CRO. There are 2 major benefits to this model. It is possible to generate the specifications in such a way that an automated build of the EDC is possible. If the system is properly validated, then the per trial level validation and user acceptance testing can be significantly reduced and the QC can be automated. In practice this means that you can have your EDC and SDTM/define.xml completely defined prior to PPFV, allowing the team to focus on trial content from that point forward.

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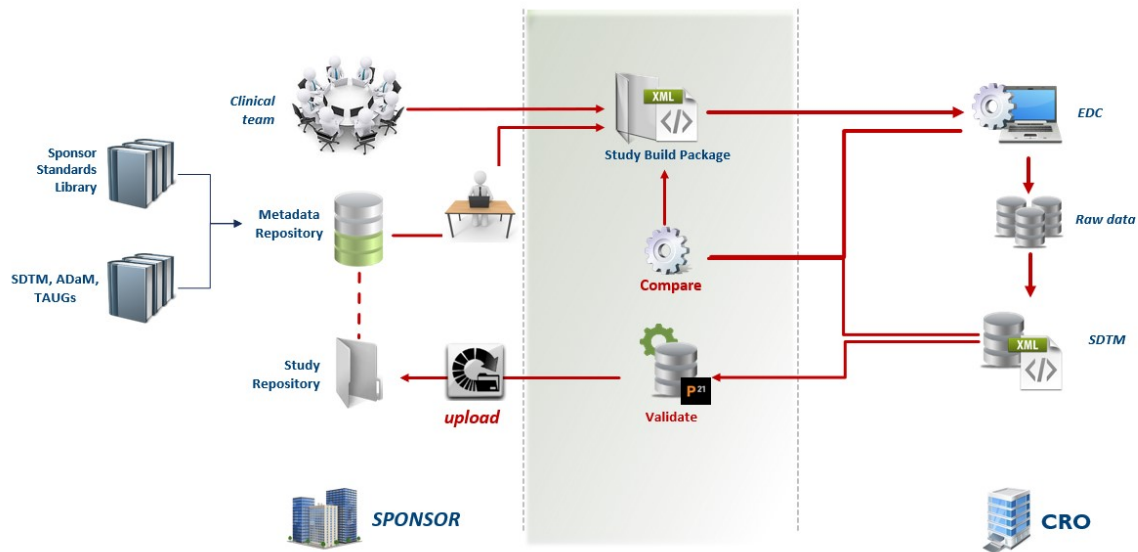


Figure 8: trial oversight and quality control of an outsourced trial with full standardization

Despite the much higher upfront investment, we were able to achieve the break-even point after 6 trials in comparison to no standardization at all. This did not take into account the activities associated with an automated study build.

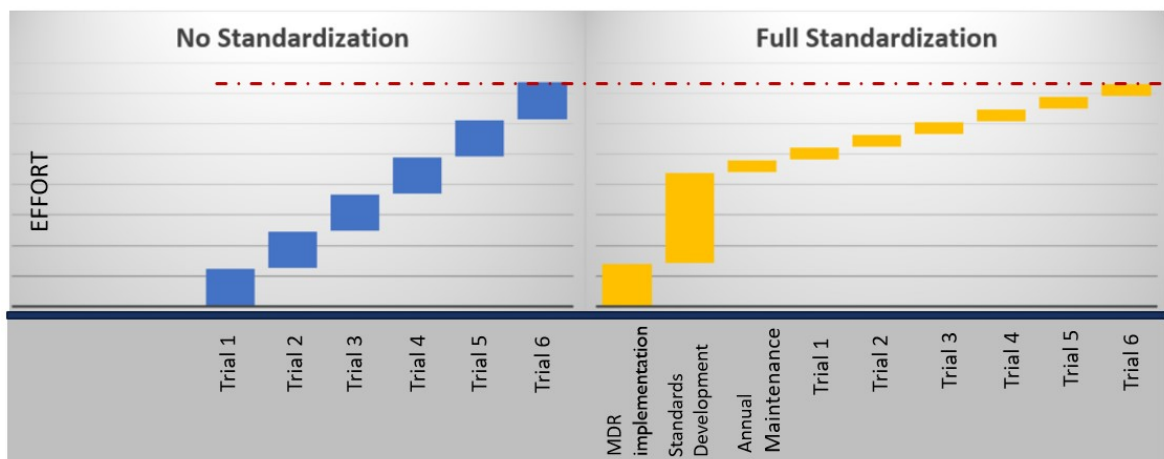


Fig 9: break-even point of advanced standardization vs no standardization

CONCLUSION

So how would you choose which level of standardization is the right level for your company? It is possible to move from one level of standardization to the next and any effort can be carried through. Figure 10 summarizes the long-term return on investment, beyond the initial break-even point. In summary, the more you standardize, the higher the quality, the higher the potential for automation and the higher the return on investment.

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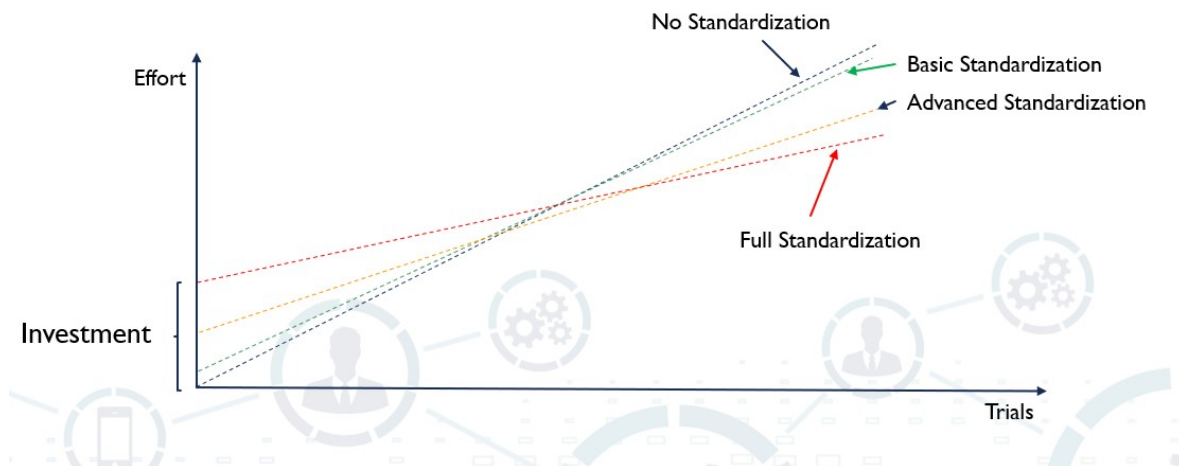


Fig 10: Return on Investment

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