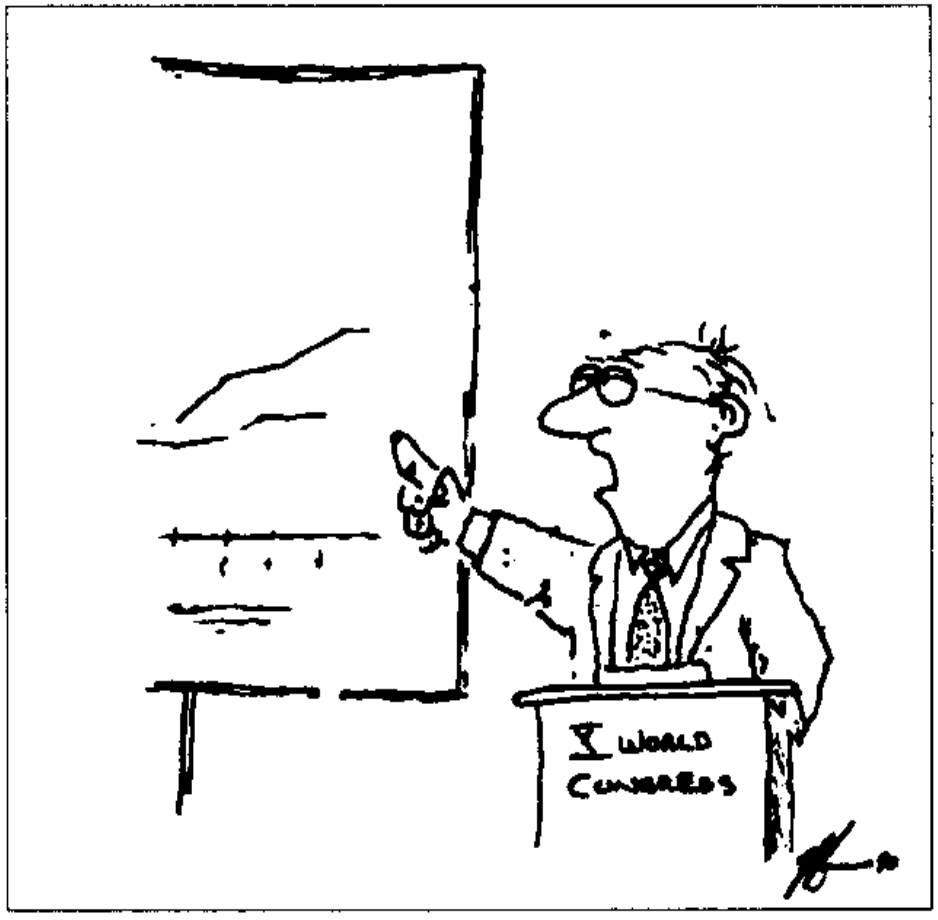
Basis of Discussion

- Trial quality can be defined
- “Large simple trials” are burdened with complexity that does not improve quality
- There are examples of trials that are much more simple and “fit-for-purpose”
- Trials could be
  - Radically simplified for answering some questions, and/or
  - Incrementally simplified in most circumstances
- Cost reductions resulting from sensible simplification can be quantified



"This randomized, double-blind trial involving over 20,000 patients was conducted over a 10 year period. Unfortunately we've forgotten why."

Selected Elements of Quality

- Adequate number of events to answer question with confidence
- In a practice setting to make results generalizable
- With proper randomization
- With reasonably complete follow-up and ascertainment of primary outcome
- With aggregate safety assessment
- With a plan for ongoing measurement, feedback, improvement of quality measures during trial conduct
- With safeguards against bias in determining clinically relevant outcomes (like blinding)
- With protection of rights of research patients

Per-Patient Clinical Trial Costs Rise 70% in Three Years

Per-patient clinical trial costs have risen an average 70 percent across all development phases since 2008. The report, "Clinical Operations: Benchmarking Per-Patient Costs, Staffing and Adaptive Design," tracks per-patient clinical trial cost benchmarks for 100 trials across multiple therapeutic areas. Cutting Edge Information compared new data with research going back to 2008 and found that Phase I per-patient costs increased by an average 46 percent and Phase II costs increased an average 72 percent.

But the largest increases in per-patient costs came in Phase IIIa and Phase IIIb, which saw an average 88 percent and 86 percent rise, respectively. The study found that both Phase IIIa and Phase IIIb per-patient costs now top $40,000 compared to approximately $25,000 three years ago. Phase IV (post-marketing studies) costs also rose, but at a more modest 31 percent, on average.

The most significant factor for increased clinical trial costs is patient recruitment. This comes as no surprise because clinical development teams have struggled to enroll sufficient volunteers to fill trials for several years now. But other factors, such as site recruitment challenges and vendor management, also play a big part in the rising costs we now see.

While finding a sufficient number of general clinical sites is a challenge, the biggest driver behind

ABOUT THIS ARTICLE:

SUBJECTS:

- Clinical Development

TYPE:

- Press Releases

TOPICS:

- clinical operations strategy
- clinical trial costs
- clinical trials patient recruitment

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SUBJECTS

Clinical Development

CLINICAL TRIALS SENSIBLE GUIDELINES CONFERENCE

Clinical Trials 2008; **5**: 38–39

Sensible guidelines for the conduct of large randomized trials

January 25-26, 2007

Sensible approaches for reducing clinical trial costs

Eric L Eisenstein[a], Rory Collins[b], Beena S Cracknell[c], Oscar Podesta[d], Elizabeth D Reid[a], Peter Sandercock[e], Yuriy Shakhov[f], Michael L Terrin[g], Mary Ann Sellers[a], Robert M Califf[h], Christopher B Granger[a] and Rafael Diaz[i]

Sensible Trial Simulation Models

(1) Full cost pharmaceutical industry

(2) Streamlined pharmaceutical industry

(3) More streamlined trial

Full Cost Model Parameters

Trial Type	Chronic Disease
Number of Patients	20,000
Number of Sites	1000
Months Duration	48
CRF Pages	60
Site Monitor Visits	24
Site Payment	$10,000

Full Cost Model Results

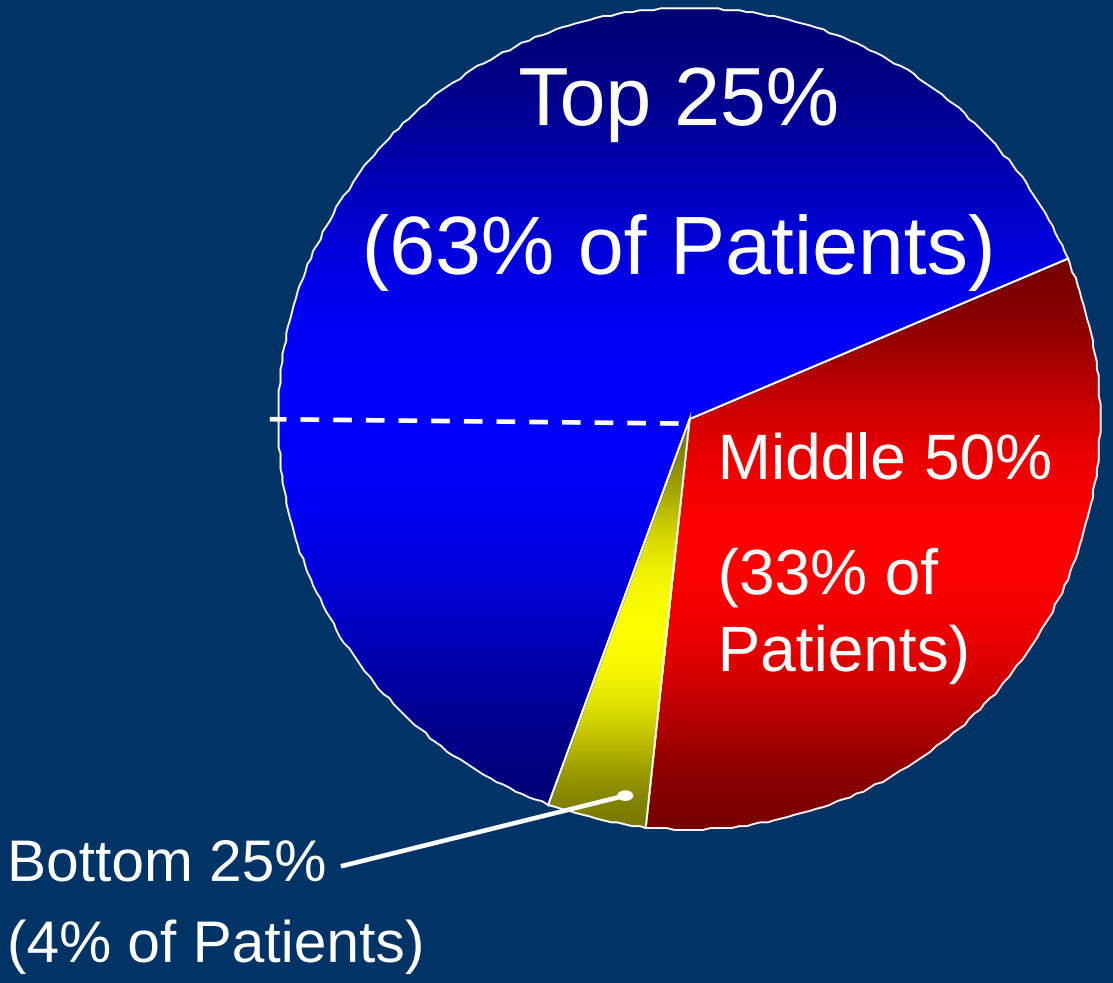
Category	Costs	Percent
Direct Labor	$167	40%
Non-labor	$255	60%
Site payments	$202	48%
Other (air, hotel, etc.)	$53	12%
Total	$421	

$US in 2007 millions

Clinical Trial Simulations

- Components varied
  - Duration (planning, enrollment)
  - Size (CRF length, number of sites)
  - Operations (EDC, site management)
- Combined model

Site Performance in Large Trials: Percent Trial Enrollment



- **Top 10% of Sites** Enroll 38% of all Patients
- **15% of Sites** Enroll 25% of all Patients
- **10–15% of Sites** Don't Enroll Patients

Berdan L, Personal communication

Cost of Start Up per Site (Sponsor costs)

Item	Sponsor $$
Start Up Grant	$3000+
Contract	$1000
Invest. Meetings	$3500
Training Materials	$300
Drug/IVRS/Lab	$2000
Reg Docs etc	$1500
Site Visit	$3000
TOTAL	$14,300 (minimum)

Simulations: Study Duration

	Planning 6 > 4 Months	Enrollment 24 > 18 Months
Total costs	**$419.8**	**$414.8**
Cost reduction	**$1.7**	**$6.7**
Percent reduction	**0.4%**	**1.6%**
Percent non-site payment	**0.8%**	**3.0%**

Simulations: CRF Length and # of Sites

	CRF Length 60 > 20 Pages	# of Sites 1000 > 750
Total costs	**$406.8**	**$385.9**
Cost reduction	**$14.7**	**$35.6**
Percent reduction	**3.5%**	**8.4%**
Percent non-site payment	**6.7%**	**16.2%**

Electronic Data Capture Assumptions

- Coordinating Center
  - 2 month reduction in close out time
  - Elimination of query processing, data entry, and medical coding
- Study Sites
  - Increase data entry time
  - Decrease query management time

Site Management Assumptions

	Full Cost Industry	Streamlined Industry
Evaluation visits	**50%**	**10%**
Site visits per site	**24**	**4**
Close-out visits	**100%**	**0%**
Source document verification	**100%**	**10%**

Simulations: EDC and Site Management

	EDC	Site Management
Total costs	**$380.2**	**$332.5**
Cost reduction	**$41.3**	**$89.0**
Percent reduction	**9.8%**	**21.1%**
Percent non-site payment	**18.8%**	**40.6%**

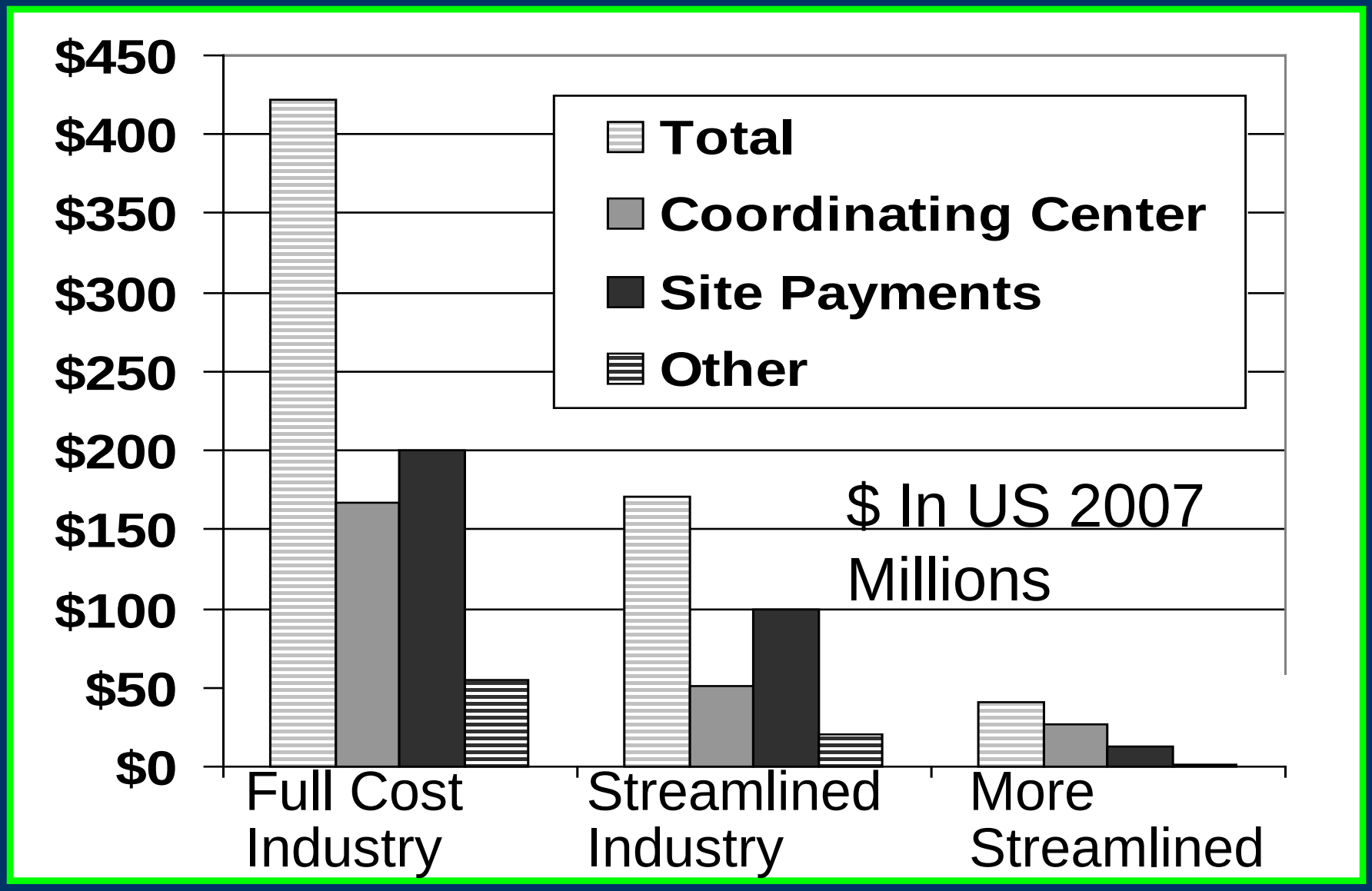
Simulations: Streamlined Industry Model

	$10k Site Payment	$5k Site Payment
Total costs	$272.4	$171.4
Cost reduction	$149.1	$250.1
Percent reduction	35.4%	59.3%
Percent non-site payment	67.9%	67.9%

More Streamlined Trial Assumptions

- Assumed previous work with all sites
  - Limit to 100 sites
  - Eliminate on-site evaluation, close-out visits, and source document verification.
- Focused case report form (5 pages)
  - Enrollment / baseline data (1 page)
  - Follow-up (4 pages, 3 questions)
- Site payment
  - $650 ($250 baseline, $100 follow-up)

Clinical Trial Cost Estimates



TASTE trial flow chart

SCAAR
SWEDEHEART

Thrombus Aspiration in ST-Elevation myocardial infarction in Scandinavia

In registry

Patients with suspected STEMI referred to primary PCI
N = 5000

↓

Enrollment

STEMI diagnosis confirmed at coronary angiography. Informed consent obtained

↓

Randomization

Online 1:1 randomization in SCAAR, guidewire advancement, i.c. nitroglycerin

↙ ↘

Thrombus aspiration and PCI | PCI alone

↘ ↙

Additional variables

Immediately after PCI: TIMI flow grade

↓

Mortality

30 days: all-cause death

↓

MI, Heart failure etc

1, 2, 5 and 10 years: all-cause death and additional secondary endpoints

Fröbert et al, AHJ 2009

SWEDEHEART - Windows Internet Explorer

https://www.reg.ucr.uu.se/swedeheart/regangiopci.jsp

Arkiv Redigera Visa Favoriter Verktyg Hjälp | Konvertera | Välj

Windows Live | Bing | Senaste aktivitet | Profil | E-post | Foton | Kalender | MSN | Dela

Favoriter | Chefens blogg | Cardiology - | Medical Jo... | Medidata RAVE | Förslag på webbplatser | Gratis Hotmail | Ladda ner fler tillägg

SWEDEHEART

Snusning	0 Aldrig varit snusare
Behandlad hypertoni	0 Nej *
Lipidsänkande medel	0 Nej *
Tidigare infarkt	0 Nej *

Angiografiska bakgrundsdata

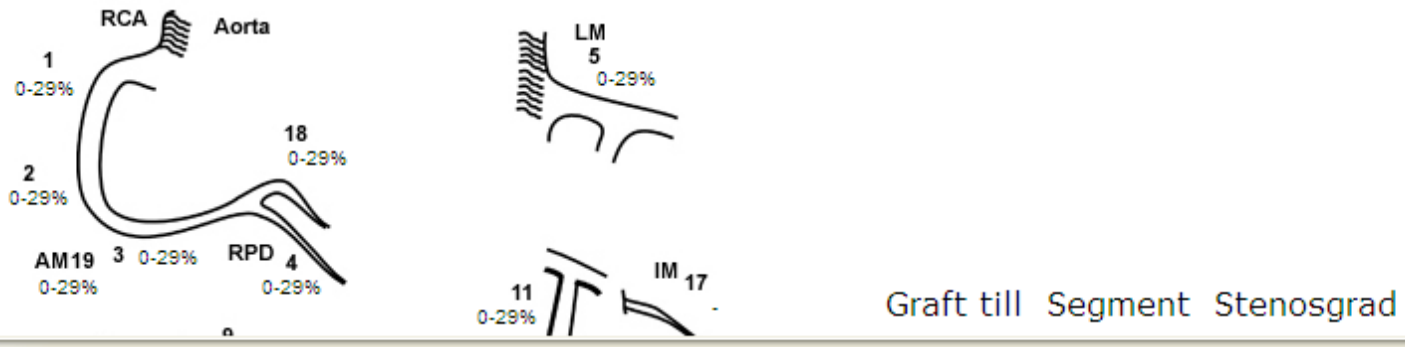
Angiograför	James, Stefan
Indikation	3 ST-höjningsinfarkt
Symtomdebut	2010-08-13 Kl. 16:30
Reperfusionsgrundande EKG	2010-08-13 Kl. 16:55
Killip klass	1 Killip I
Punktionställe	5 A radialis höger
Punktionsdatum och klockslag	2010-08-13 * 17:25

When PCI with indication

STEMI-primary/rescue PCI
and
PCI ad hoc
is registered the system
proposes randomization

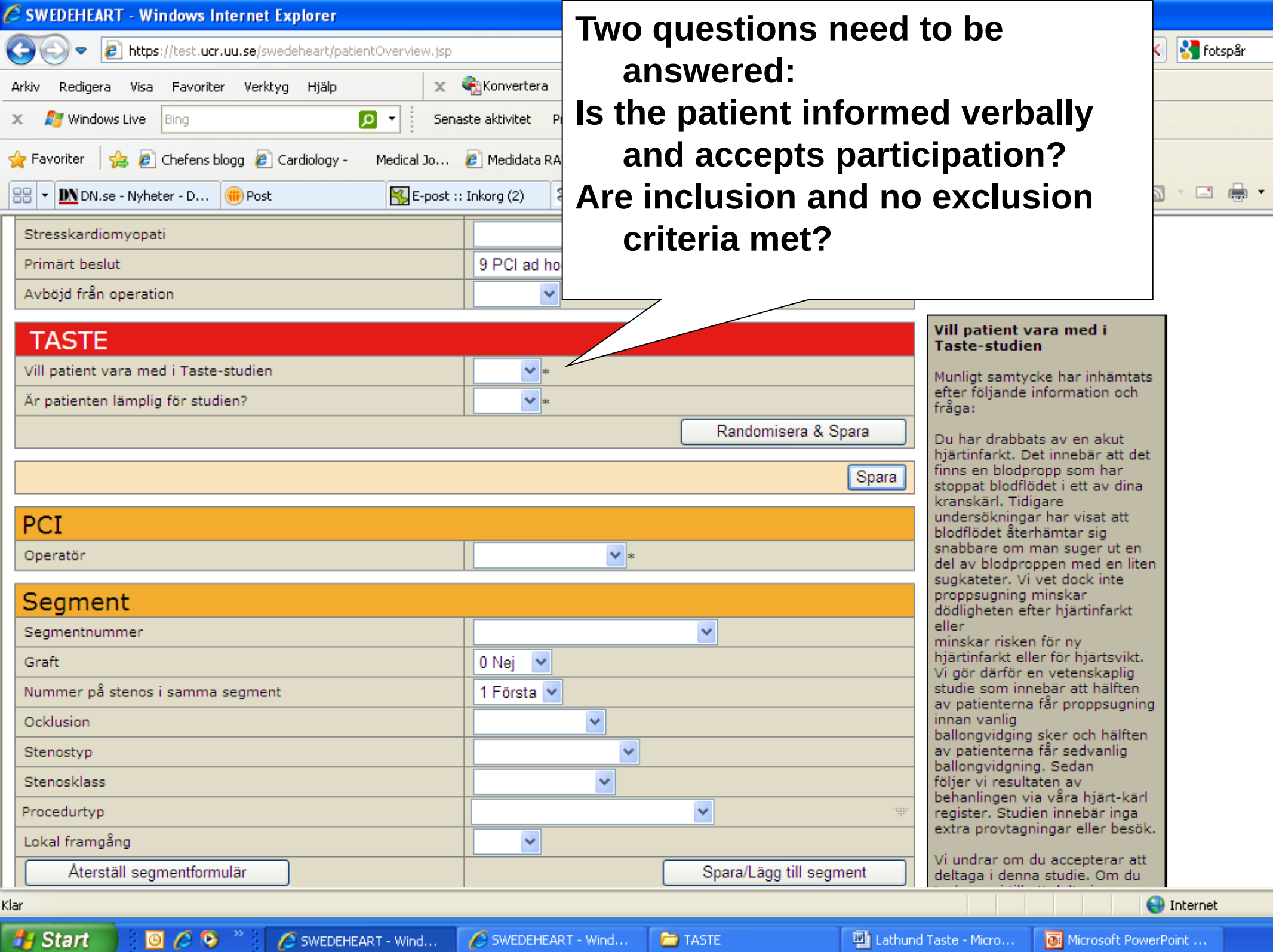
Angiografi

Angiografiskt fynd



Klar | Internet

Start | Swedeheart - Windo... | SWEDEHEART - Wind... | TASTE | Lathund Taste - Micro... | Microsoft PowerPoint ...


SWEDEHEART - Windows Internet Explorer
https://test.ucr.uu.se/swedeheart/patientOverview.jsp
Arkiv Redigera Visa Favoriter Verktyg Hjälp
Konvertera
Windows Live
Bing
Senaste aktivitet
Favoriter
Chefens blogg
Cardiology -
Medical Jo...
Medidata RA
DN.se - Nyheter - D...
Post
E-post :: Inkorg (2)
Two questions need to be answered:
Is the patient informed verbally and accepts participation?
Are inclusion and no exclusion criteria met?
Stresskardiomyopati
Primärt beslut
9 PCI ad ho
Avböjd från operation
TASTE
Vill patient vara med i Taste-studien
Är patienten lämplig för studien?
Randomisera & Spara
Spara
PCI
Operatör
Segment
Segmentnummer
Graft
0 Nej
Nummer på stenos i samma segment
1 Första
Ocklusion
Stenostyp
Stenosklass
Procedurtyp
Lokal framgång
Återställ segmentformulär
Spara/Lägg till segment
Vill patient vara med i Taste-studien
Munligt samtycke har inhämtats efter följande information och fråga:
Du har drabbats av en akut hjärtinfarkt. Det innebär att det finns en blodpropp som har stoppat blodflödet i ett av dina kranskärl. Tidigare undersökningar har visat att blodflödet återhämtar sig snabbare om man suger ut en del av blodproppen med en liten sugkateter. Vi vet dock inte proppsugning minskar dödligheten efter hjärtinfarkt eller
minskar risken för ny hjärtinfarkt eller för hjärtsvikt. Vi gör därför en vetenskaplig studie som innebär att hälften av patienterna får proppsugning innan vanlig
ballongvidging sker och hälften av patienterna får sedvanlig ballongvidgning. Sedan följer vi resultaten av behanlingen via våra hjärt-kärl register. Studien innebär inga extra provtagningar eller besök.
Vi undrar om du accepterar att deltaga i denna studie. Om du
Klar
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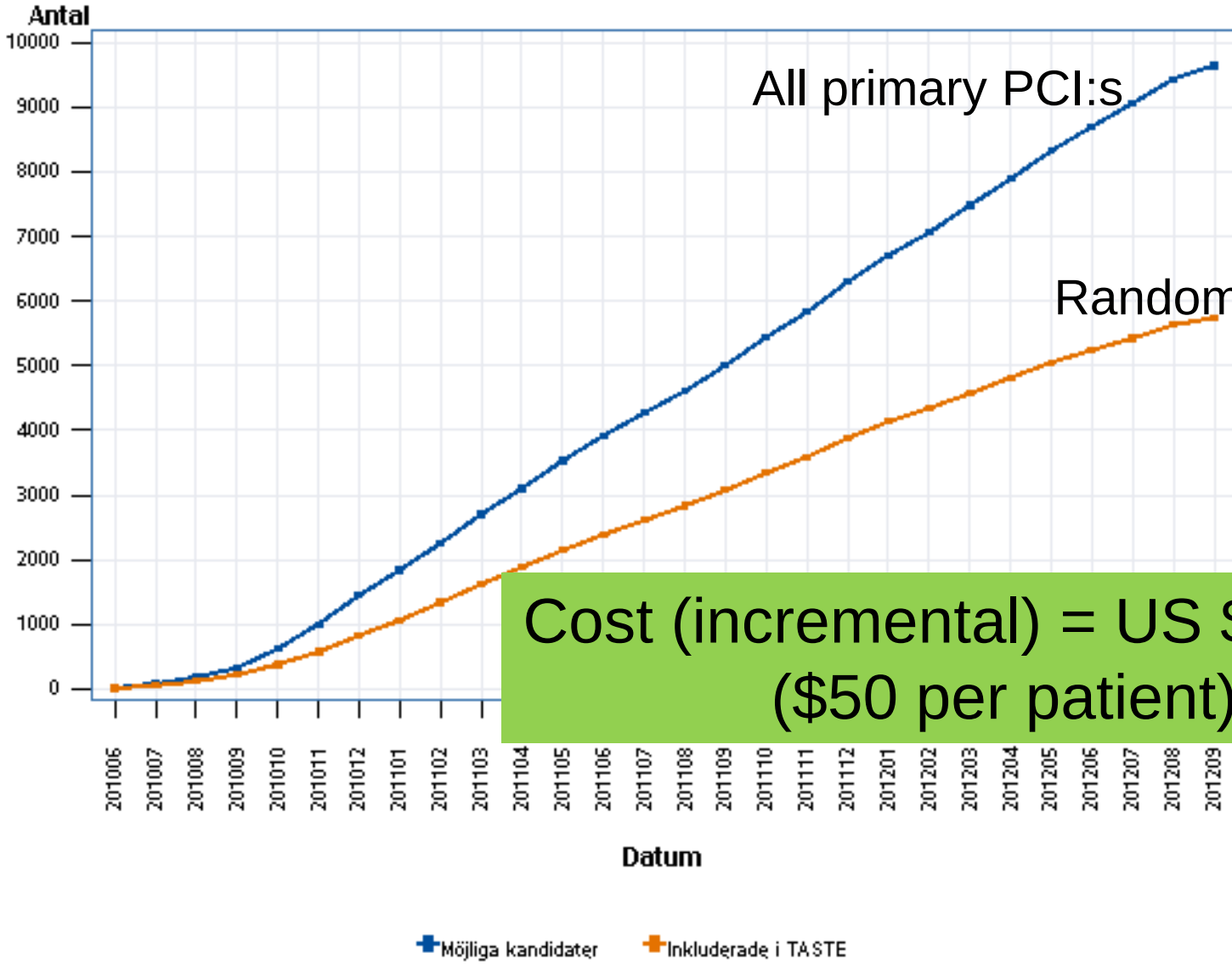
SWEDEHEART - Wind...
TASTE
Lathund Taste - Micro...
Microsoft PowerPoint ...

Inclusion rate



Cost (incremental) = US $300,000
($50 per patient)

If one could save $100's of millions without reducing quality, why hasn't it already been done?

- Risk aversion
  - Regulatory leaders say one thing (simplify) but reviewers and auditors do another (ask for everything)
  - Better to collect 100 unnecessary variables than miss one important one
- Regulatory departments and CRO's promote the *status quo*
- Lack of international harmonization forces use of the most complicated common denominator

Concluding thoughts

1. Each trial is different and thus there are no universal answers. Opportunities vary for types of sponsor, treatment studied, stage of development, risks, etc.
2. Substantial reductions in the costs of large-scale clinical trials can be achieved without compromising quality.
   - Incremental
   - Transformative
3. We need research on the impact of simplifying clinical trials.