From:	Cagen, Stuart Z SCC-CF-SS <stuart.cagen@shell.com>
Sent:	Thursday, June 23, 2005 10:21 PM (GMT)
To:	Cagen, Stuart Z SCC-CF-SS <stuart.cagen@shell.com>; Tsai, Shan P SHLOIL-SHS <Shan.Tsai@shell.com>; Clegg, Patsy M SCC-CHSE-PC <patsy.clegg@shell.com>
Subject:	FW: BHRC-TC... Handout for EA Conf Call - Fri 12/10, 11am EST
Attach:	121004 DRAFT SHS EA ver 4.ppt

Memories... Of possible use for the call tomorrow morning. Looks like there will be a combined call tomorrow, with Otto joining the call with Tom, et al at 930 am Houston time

Stuart Cagen

Shell Chemical LP
One Shell Plaza, 910 Louisiana, Houston, TX 77002-4916

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Email: stuart.cagen@shell.com
Internet: http://www.shell.com/chemicals

"Business Success through HSSE Excellence"

-----Original Message-----
From: Bruce Jarnot [mailto:jarnotb@api.org]
Sent: Thursday, December 09, 2004 5:47 PM
To: benzconsort-tc@listserve.api.org
Cc: Lorraine Twerdok; Howard Feldman
Subject: BHRC-TC... Handout for EA Conf Call - Fri 12/10, 11am EST

Attached is Tom Armstrong's handout (ppt file) for Friday morning's Exposure Assessment conference call...

Best Regards - Bruce.

-----Original Message-----
From: Bruce Jarnot
Sent: Tuesday, December 07, 2004 10:50 AM
To: benzconsort-tc@listserve.api.org
Cc: Howard Feldman
Subject: BHRC-TC... REMINDER - EA Conf Call - Fri 12/10, 11am EST
Importance: High

Benzene Health Research Consortium (BHRC) Technical Committee -

REMINDER... we have a conference call scheduled this Friday, Dec 10th, to review Exposure Assessment (EA) progress in the Shanghai Health Studies with Tom Armstrong, Rob Schnatter and Yimei Zhou:

Date: Friday, Dec 10

Time: 11:00am - 2:00pm EST

Dial-in: 763/315-6900 (or toll free 866/448-6756)

PIN code: 6828319#

Best Regards - Bruce.

*****

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Regulatory and Scientific Affairs
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Review of SHS Exposure Assessment

10 December 2004

Tom Armstrong

Rob Schnatter

Yimei Zhou

Overall Study Aims and Values

Case Control (PI: Otto Wong / Fu Hua)

- Is NHL associated with benzene?
  - If so, is NHL / benzene specific to NHL subtype?
- What is shape of dose-response curve for NHL and AML?
- Provide comment on NCI NHL / benzene study

Disease Progression (PI: Rich Irons / Fu Hua)

- Does benzene-induced disease have a distinct pattern?
- Does benzene-induced cancer progress through requisite steps?
- What is shape of dose-response curve for MDS and AA?
- May have impact on “safe” levels

Molecular Epidemiology (PI: Rich Irons / Fu Hua)

- What is shape of dose-response for blood effects? (Phase 1, 2A)
- What is earliest marker for effects? (Phase 1, 2A, 2B)
- Does benzene induce toxicity more readily in susceptible workers? (Phase 2A, 2B)
  - Provides mechanistic insight; possible protection strategy in some settings
- Are there requisite steps for later markers (blood count decrements)? (Phase 2A, 2B)
- Does benzene act on bone marrow differently than peripheral blood? (Phase 2B)
  - If so, provides insight on mechanisms, thresholds
  - Could provide new basis for dose-response

Study Positives

State-of-the-art lab

- Improved diagnostic capabilities
- New WHO scheme for LH disease classification enabled
- Tissue storage allows future research
- Patient population directly benefiting from improved diagnoses / treatment
- Reputation for diagnosis reflected by more signatory hospitals

Unique resource for research

- Preliminary results already suggest threshold for blood effects
- Preliminary results suggest bone marrow changes in absence of peripheral blood
- Could be unique benzene signature for myelodysplasia
- Enhancing IH capabilities in Shanghai / China

Comments / review

- Study obtained positive feedback at recent worldwide conference
- Esteemed SRP and ERB has favorably reviewed study
- Study may be helping to reduce benzene exposure in Shanghai

EA Progress Summary

	CC/DP	BP	ME I	ME IIA	ME IIB
Planned Recruitement Total	5400	50	2000	1000	200
Planned Recruitment YTD	3150	22	896	448	133
Actual Recruitment YTD	2328	32	192	230	3
Outlook (w/o + $$)	5310	50	852	518	10?
Outlook (w + $$)	6730	>50	2000	1000	100-200?
Planed EA (Bnz) Total	540	50	2000	1000	200
Planned EA (Bnz) YTD	315	22	192	448	-
Actual Prelimenary EA (Bnz) YTD	84	32	192	230	-
Actual Final EA (Bnz) YTD	50	22	192	230	-
Percentage EA Quantitative	??	~100%	~100%	100%	100%
Prevalence BNZ Exposure	5%	100%	100%	100%	100%
Outlook (w/o + $$)	160	50	852	518	10?
Outlook (w + $$)	202	>50	2000	1000	100-200?
	CC	BP	ME	ME II total	
Factory Recruited	27	1	1	5	
No. of EA Samples	300+	900	N/A	5000+	

Deliverables Associated with Each Study

Molecular Epidemiology

Scope		EMBSI Activities / Deliverables	Status	Actual Effort
		Design	Complete	+5%
		Questionnaires Design	Complete	-
		Training of staff	Complete	(see CC)
		Abstraction forms	Complete	-
		Factory selection	In progress	2X
		Exposure assessment	In progress	(see CC)
		QA / QC	In progress	-
		Statistical analysis	Future	Future
		Publication assistance	Future	Future
		Presentations assistance	Future	Future
Phase 1:	2000 workers			
Phase 2A:	1000 workers			
Phase 2B:	200 workers			

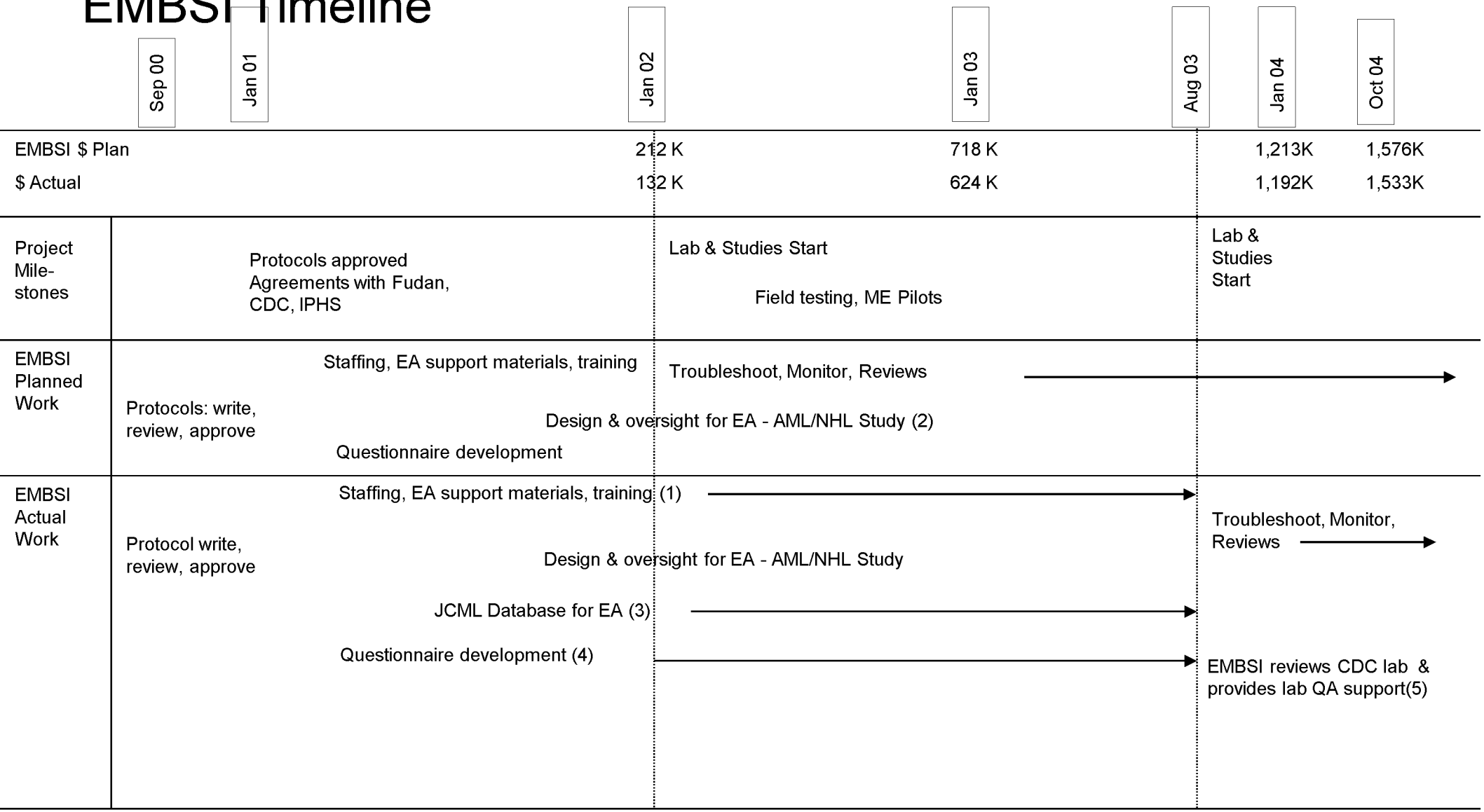
Deliverables Associated with Each Study (cont'd)

Disease Progression / Case Control

Planned Scope	
BZ poisoning cases:	50
Aplastic anemia:	250
MDS:	300
AML:	600
NHL:	600
Controls:	3600
Total:	5400

EMBSI Activities / Deliverables	Status	Actual Effort
Design	Complete	+20%
Questionnaires design	Complete	+60–70%
Training of staff	Complete	Retune +30%
- Quest. administrators	Complete	"
- Clinical coordinators	Complete	+ 20-30%
- Exposure Assessment	Complete	"
Control selection	Complete	+20–30%
Exposure assessment	In progress	+2-3X
QA / QC	In progress	In progress
Some statistical analysis (DP)	Future	Future
Some publications (DP)	Future	Future
Some presentations (DP)	Future	Future

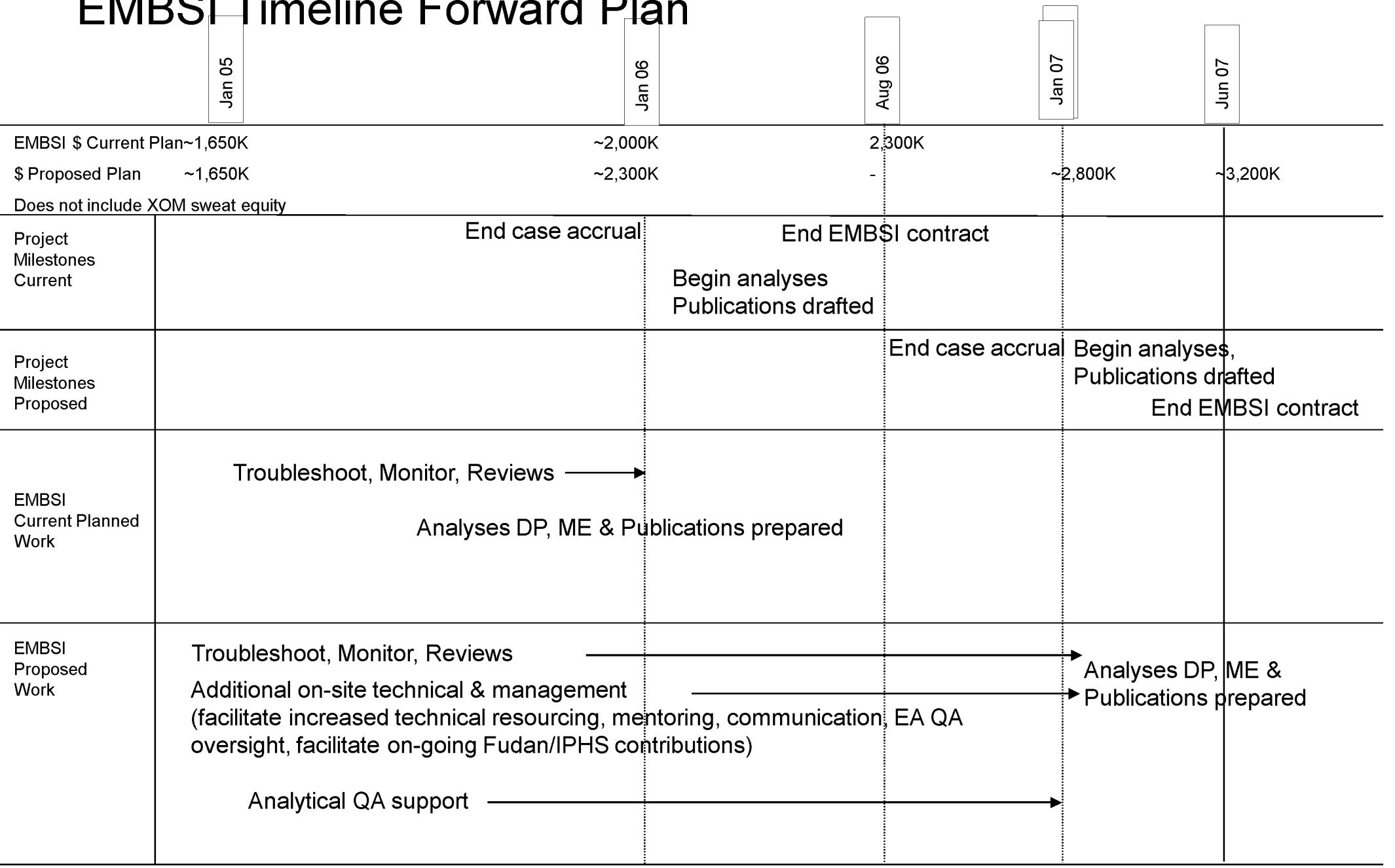
EMBSI Timeline



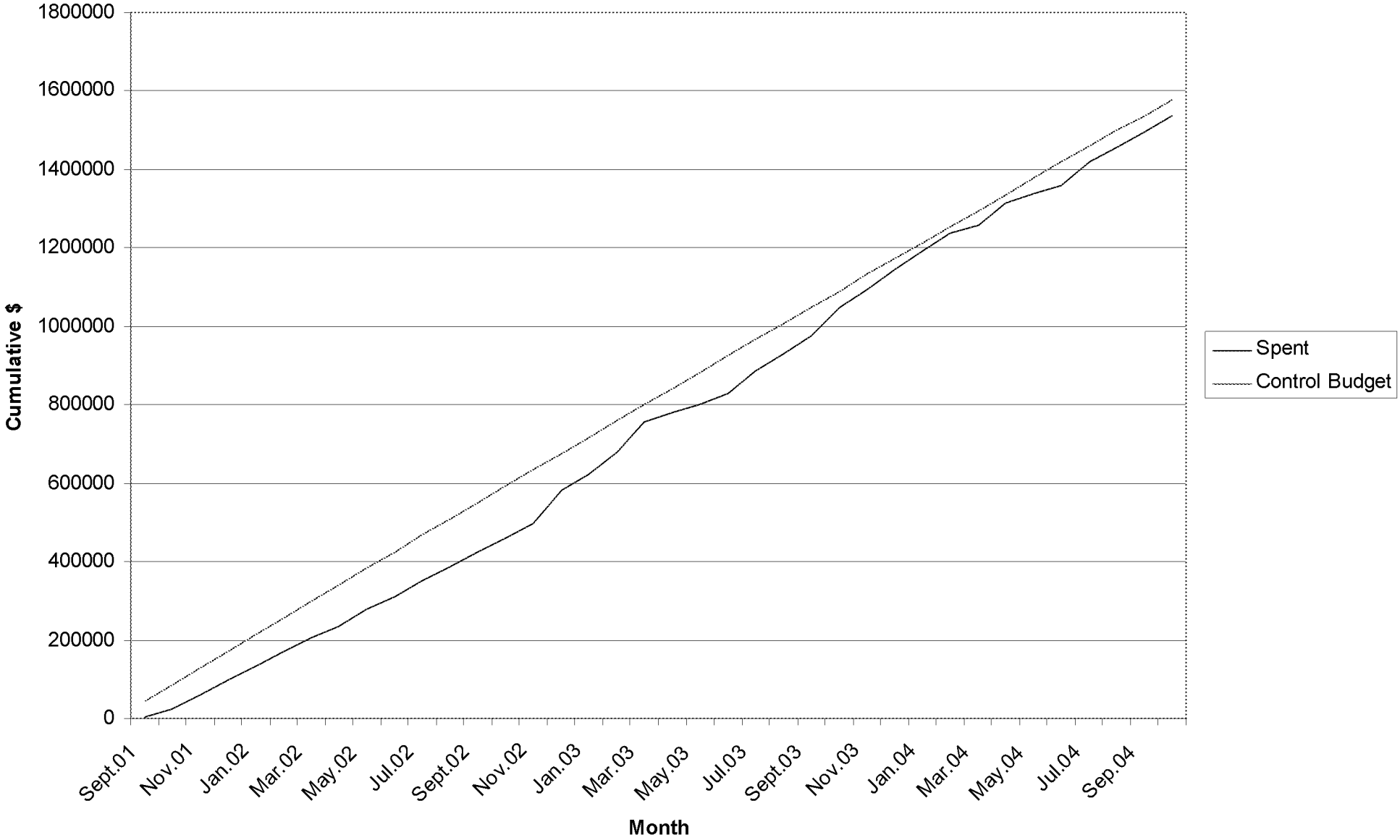
Notes: (1) Extended due to project start delays, changing agreements and Fudan staff reassignments
(2) Added per SRB request and budget increased
(3) Need identified by PI Team
(4) Extended due to add in of AML/NHL Study EA support
(5) Unanticipated need covered by EMBSI

DRAFT

EMBSI Timeline Forward Plan



SHS EMBSI BUDGET

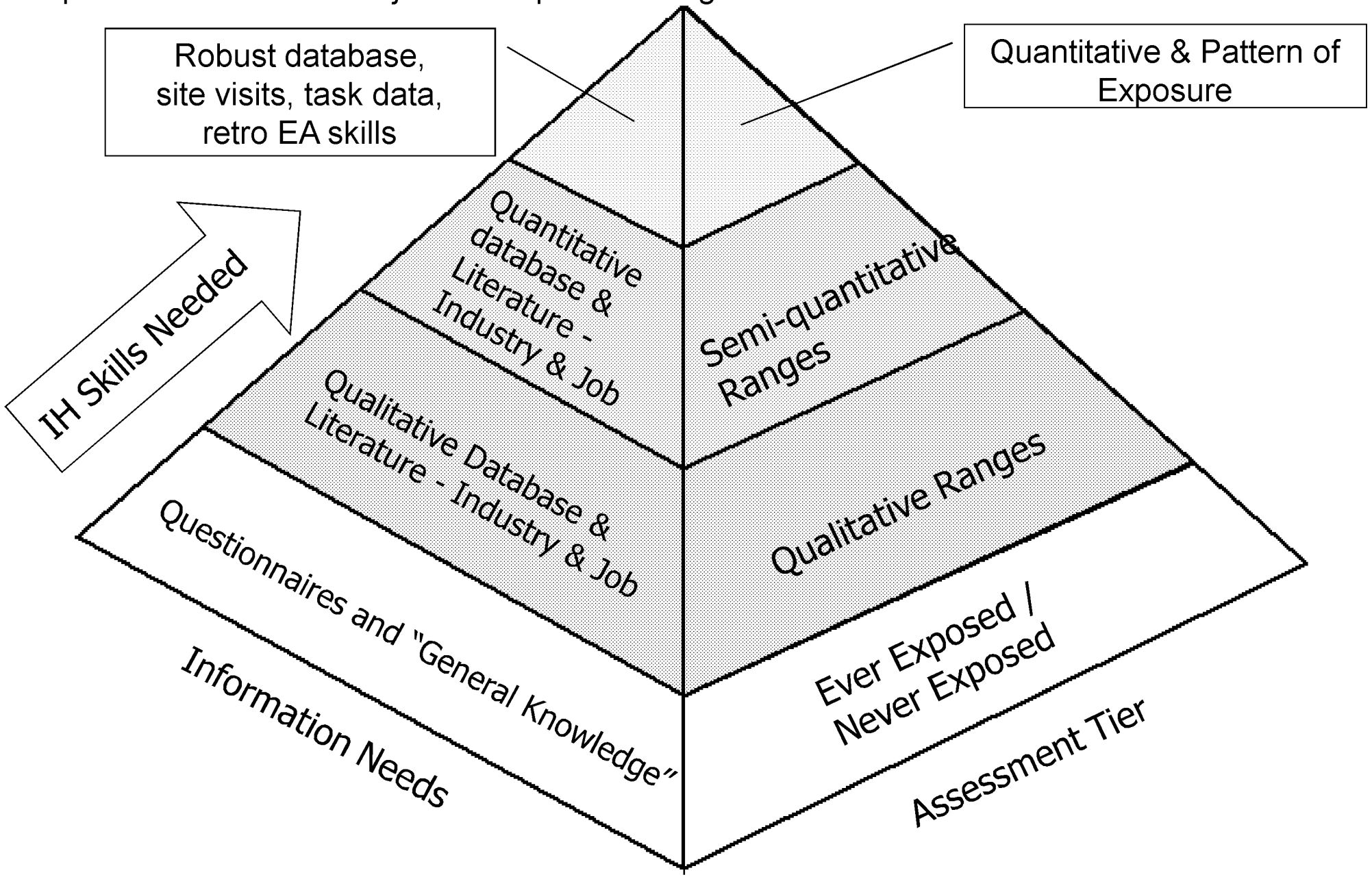


Exposure Assessment Options

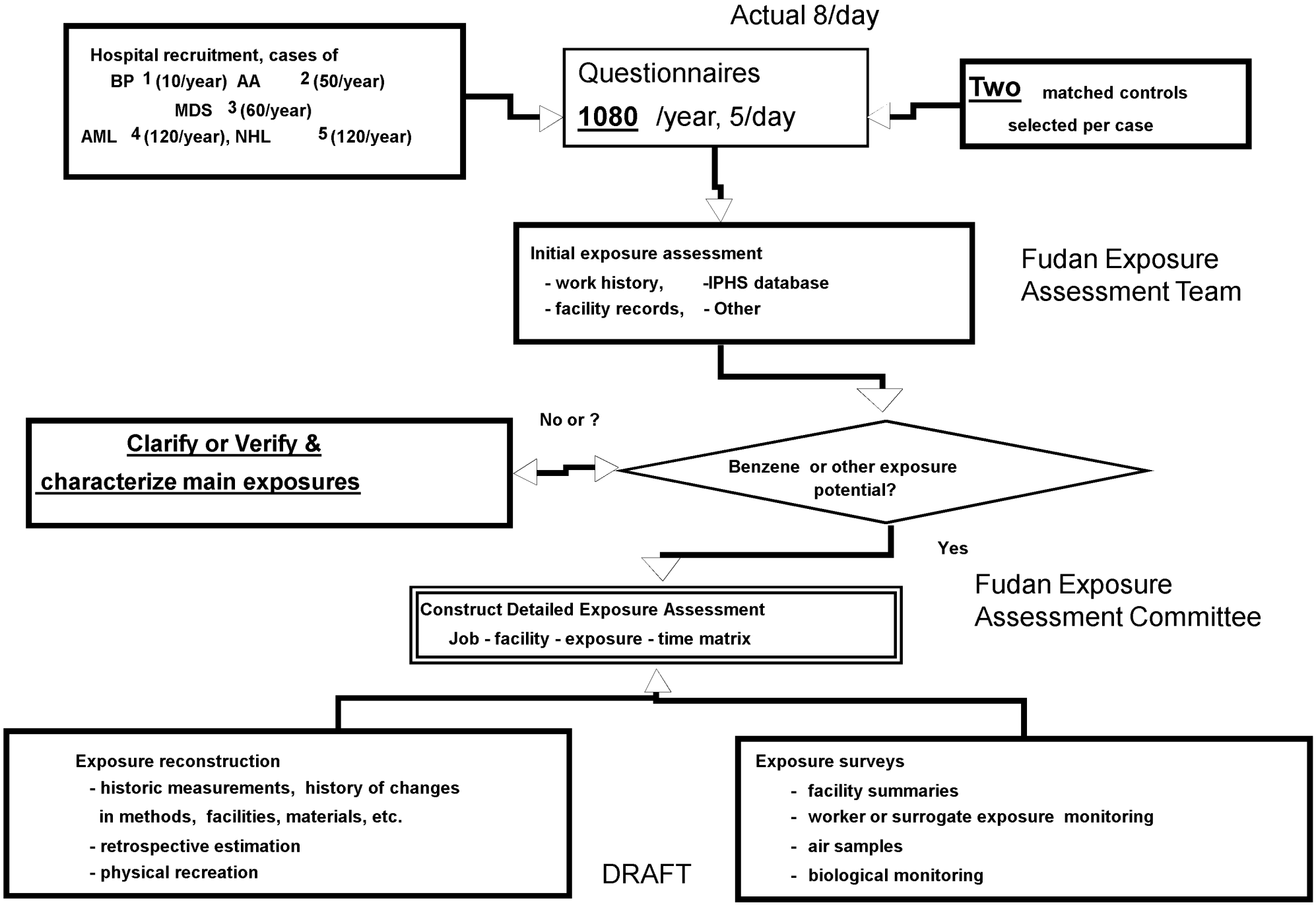
Review of strategies and study impacts

Case Control Studies Tiered Design:

Expectation of Fewer Subjects Completed at Higher Tiers



CC / DP Exposure Assessment Design

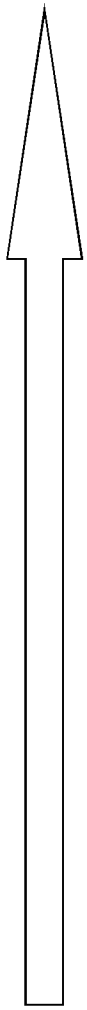


EA Tiers: Design Basis for SH Studies

	Case Control Studies AML/NHL, Broad DP (1)	DP Case Series (1)	ME Studies (2)	
			Phase 1	Phase 2A Phase 2B
Quantitative	•Quantitative dose-response •Links to studies used in risk assessments	•Quantitative dose-response •Links to studies used in risk assessments	Underway as planned Quantitative dose-response Links to studies used in risk assessments	
Semi-Quantitative Ranks	•Semi-quant. "dose" response •Semi-quant. causal link •Semi-quant. link to studies used in risk assessments	•Semi-quant. "dose" response •Semi-quant. causal link •Semi-quant. link to studies used in risk assessments	•Semi-quant. "dose" response •Semi-quant. causal link •Semi-quant. link to studies used in risk assessments	
Qualitative Ranks	Group differences in risk	Group differences in risk		
Ever Exposed Never exposed	Association with disease	Association with disease		

Note 1: For the CC/DP studies, all tiers have a "certainty" rating and these generally decrease at the higher tiers
Note 2: "lower tiers" not planned or needed in the ME studies. Semi-quantitative ranks may be applied in some factories for Phase 1, but full quantitative assessment planned.

CC/DP Studies - Bz EA Impact Analysis

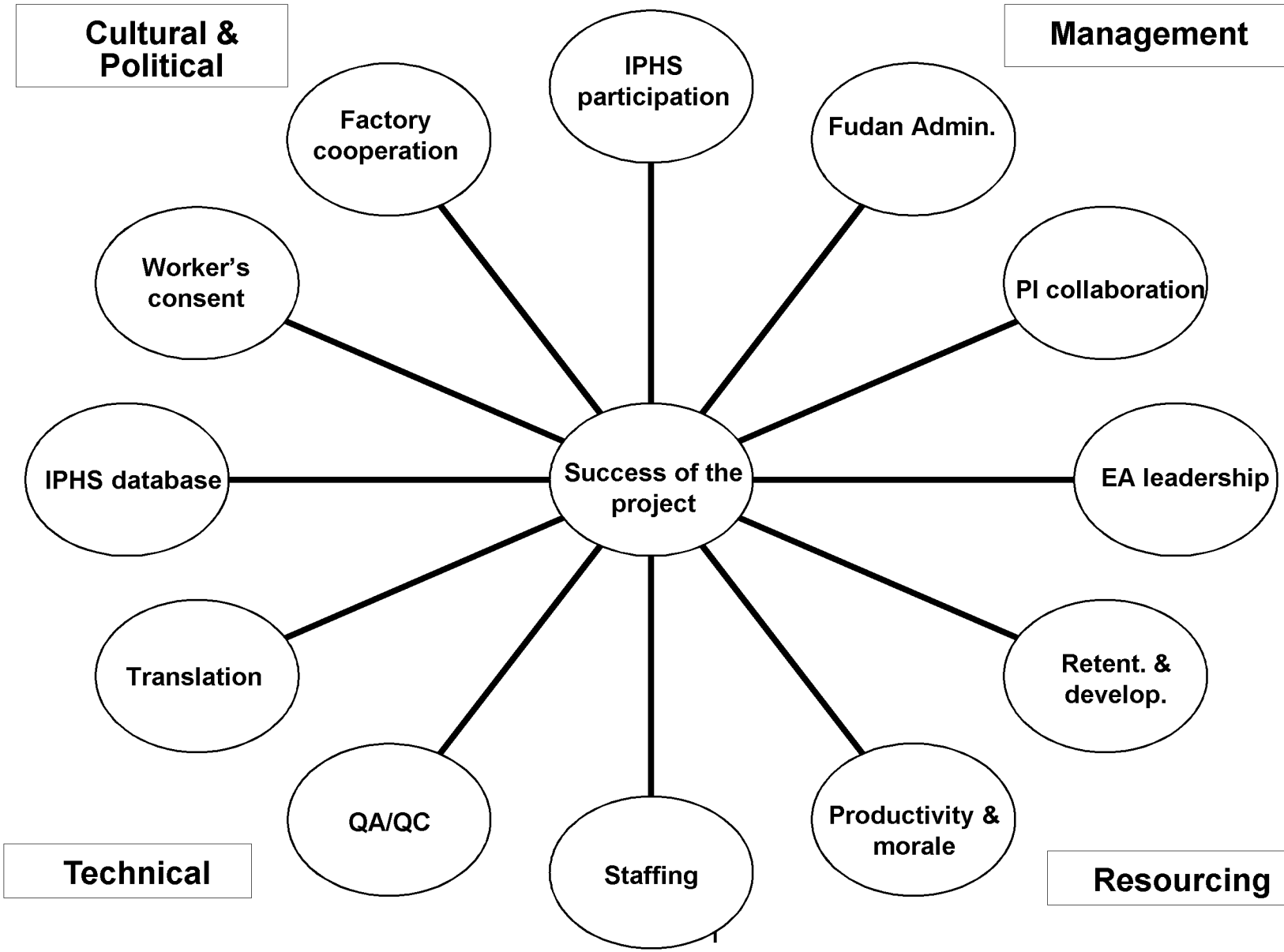


Read Here to Top

Stop Point	Study Impact	Discussion
Quantitative	•Best evidence of causal links •Data for use in risk assessment •Currently planned for ~10% of subjects	•Requires additional investigative effort for site reviews, additional retrospective EA skills, robust analysis of IPHS database and other quantitative data sources •Most difficult tier to complete •Costs - medium - high •Probability of Success - low •Value -high
Semi Quantitative 0 - 0.3 mg/m3 0.3 to 3 3 to 40 > 40	•Improved evidence of causal links •Semi-quant. link to quantitative risk assessments	•Work site screening visits •Difficulty - medium •Costs - medium •Probability of Success - medium •Value - medium
Qualitative range No Low Medium High	•Risks by groups for stronger information or possible causal link for diseases of concern	•Difficulty - low - medium •Costs - low •Probability of Success - high •Value - low-medium
Ever exposed, never exposed	•Only potential relationship of benzene or other exposures to diseases of concern	•Questionnaire driven •Difficulty - low •Probability of Success - high •Value - low

Go-forward Options

Many Factors Lead to Project Success



Opportunities

Action Item	Expected Benefits	Implementor	Enabler
#1 *YZ assignment to Shanghai and more EA support*	EA staff morale, productivity, leadership; understanding Fudan / IPHS drivers, EA qualifications, less EA staff resource diversion	EMBSI	Technical/Oversight Committees FU's support PI involvement in EA
#2 *Fund extension of the study*	Increase subject numbers, more insight on disease mechanisms (from ME/DP), more power for case control less chance of spurious findings	Oversight Committee	Technical/Oversight Committees Factory access through IPHS
#3 *Re-engage IPHS*	More efficient factory selection, EA, more insight on IPHS database limitations	PI's	PA/Member Companies
#4 *Further support the Fudan team*	Continuous Improvement of PI collaboration, YZ effectiveness, post-study prob. of lab utilization	Oversight Committee	Technical/Oversight Committees
#5 *Perform independent QA/QC audits of Fudan IH laboratory and field (questionnaire EA) work*	Ensure data integrity	Member CO's, external resource	Technical Committee

Recommendations:
Maintain Full Scope of SHS

- Continue Planned Quantitative EA for CC/DP Studies
- Continue Recruitment of Subjects for ME IIB
- Maximizes Value of Study Results for Risk Assessments
- Requires Extension through 2007
- Requires Additional $3.3M Funding