

From: Clegg, Patsy M SCC-CHSE-PC <patsy.clegg@shell.com>
Sent: Monday, March 15, 2004 7:16 PM (GMT)
To: Richard.Irons@UCHSC.edu; Otto Wong (E-mail) <ottowong@sol.com>; Fu (E-mail) <hfu@shmu.edu.cn>
Cc: Brian Doll (E-mail) <brian.e.doll@exxonmobil.com>; Burnett, Don (E-mail) <burnetdm@bp.com>; Cagen, Stuart Z SCC-HSE <stuart.cagen@shell.com>; Lynn Russo (E-mail) <lynn.b.russo@exxonmobil.com>; Michael Johnston <Mike.d.Johnston@ConocoPhillips.com>; Patrick Beatty <PatrickBeatty@chevrontexaco.com>; Twerdok, Lorraine (E-mail) <twerdokl@api.org>; Bruce M. Jarnot (E-mail) <jarnotb@api.org>; Christopher Roythorne (E-mail) <chris.roythorne@uk.bp.com>; Jennifer Galvin (E-mail) <jennifer.b.galvin@conocophillips.com>; Michael Bird (E-mail) <michael.g.bird@exxonmobil.com>; Tsai, Shan SP SHLOIL-SHLOIL-HE <Shan.Tsai@shell.com>; Stephen Bowes (E-mail) <stephen.m.bowes@exxonmobil.com>; Colletti, Sarah J SCC-CSEA <sarah.colletti@shell.com>; Iannarone, Lauren B SCC-CSEA <Lauren.Iannarone@shell.com>; Jay Stuller (E-mail) <sjay@chevron.com>; Matthew Todd (E-mail) <toddm@api.org>; Myron Harrison (E-mail) <myron.c.harrison@exxonmobil.com>; Richard Herold (E-mail) <heroldra@bp.com>; Valerie Crissey (E-mail) <vcrissey@chevrontexaco.com>; John Wagner (E-mail) <wagner@api.org>; Mark Fitzsimmons (E-mail) <mfitzsim@steptoe.com>
Subject: RE: 2005 Shanghai Health Study Annual Meeting in Shanghai

Gentlemen,

Richard has suggested the 1st week in November, 2005 for the Shanghai Health Study annual meeting in Shanghai. Is this agreeable with you? We should confirm that we are agreeing the week of Oct 30 - Nov 4, with the meeting starting on Tuesday, Nov 1. Or are we considering the week commencing Nov 7, with the meeting starting on Tuesday, Nov 8. My preference is the week of Oct 30, however, either is fine.

Regards,
Patsy

Patsy Clegg
Product Steward
Shell Chemical LP
One Shell Plaza, 910 Louisiana, Houston, TX 77002-4916

Tel: +1 713 241 2521 **Fax:** 3325
Email: patsy.clegg@shell.com
Internet: <http://www.shell.com/chemicals>

-----Original Message-----

From: Richard.Irons@UCHSC.edu [mailto:Richard.Irons@UCHSC.edu]
Sent: Monday, March 15, 2004 12:46 PM
To: Clegg, Patsy M SCC-CHSE-PC
Subject: RE: 2005 Shanghai Health Study Annual Meeting in Shanghai

Dear Patsy,

The best time for me would be the first week in November, 2005.

SHELL-MCCLURG-054542

Jane Liu is my administrative assistant in Shanghai. She is a very good resource for information and advice on "where, how, why, when and how much? However, she doesn't have sufficient time to make all of the arrangements. We would need additional help. My rule of thumb is in China time it takes 3X the amount of time required in the US to get anything done, and it is the same with personnel!

Best regards,

Richard

[Irons Richard] -----Original Message-----

From: Clegg, Patsy M SCC-CHSE-PC [mailto:patsy.clegg@shell.com]

Sent: Tuesday, March 09, 2004 6:04 AM

To: Irons Richard; Otto Wong (E-mail); Fu (E-mail)

Cc: Brian Doll (E-mail); Burnett, Don (E-mail); Cagen, Stuart Z SCC-HSE; Lynn Russo (E-mail); Michael Johnston; Patrick Beatty; Twerdok, Lorraine (E-mail)

Subject: 2005 Shanghai Health Study Annual Meeting in Shanghai

Gentlemen,

The BHRC (Benzene Health Research Consortium) is very excited about coming to Shanghai for the annual meeting in 2005. We are asking for your help for two things.

1. The date for the 2005 meeting. We are proposing to meet either the last week of September or the first week in November. We are not considering the month of October because of religious holidays that could preclude some from attending. Would you please discuss amongst yourselves and confirm back to me your choice of dates. We would like to be able to announce the 2005 meeting dates at our 2004 meeting this August (invitations will be sent very soon).

2. Contact person in China. To facilitate planning for the 2005 meeting in Shanghai, we would appreciate it if you would name a focal point. This person would assist API and the consortium in making meeting arrangements, such as a location.

Thank You in advance for your assistance.

Regards,
Patsy

Patsy Clegg
Product Steward
Shell Chemical LP
One Shell Plaza, 910 Louisiana, Houston, TX 77002-4916

Tel: +1 713 241 2521 **Fax:** 3325

Email: patsy.clegg@shell.com

Internet: <http://www.shell.com/chemicals>

Review of SHS Exposure Assessment

10 December 2004

Tom Armstrong

Rob Schnatter

Yimei Zhou

DRAFT

1

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 Recruitment Total	5400	50	2000	1000	200
Planned Recruitment YTD	3920	22	1104	552	133
Actual Recruitment YTD	2328	32	192	230	3
Outlook (w/o + \$\$)	4213	50	348	417	10?
Outlook (w + \$\$)	5953	>50	2000	1000	100-200?
Planned EA (Bnz) Total	540	50	2000	1000	200
Planned EA (Bnz) YTD	392	22	1104	448	-
Actual Preliminary EA (Bnz) YTD	84	32	192	230	-
Actual Preliminary EA (Others) YTD	541	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 + \$\$)	211	50	348	417	10?
Outlook (w + \$\$)	298	>50	2000	1000	100-200?
	CC	BP	ME	ME II total	
Factory Recruited	37	1	1	5	
No. of EA Samples	300+	900	N/A	5000+	

DRAFT

Deliverables Associated with Each Study

Molecular Epidemiology

		EMBSI Activities / Deliverables	Status	Actual Effort
Scope Phase 1: 2000 workers Phase 2A: 1000 workers Phase 2B: 200 workers		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

Deliverables Associated with Each Study

(cont'd)

Disease Progression / Case Control

		EMBSI Activities / Deliverables	Status	Actual Effort
Planned Scope		Design	Complete	+20%
		Questionnaires design	Complete	+60–70%
		Training of staff	Complete	Retune +30%
		- Quest. administrators	Complete	“
BZ poisoning cases: 50		- Clinical coordinators	Complete	+ 20-30%
Aplastic anemia: 250		- Exposure Assessment	Complete	“
MDS: 300		Control selection	Complete	+20–30%
AML: 600		Exposure assessment	In progress	+2-3X
NHL: 600		QA / QC	In progress	In progress
Controls: 3600		Some statistical analysis (DP)	Future	Future
Total: 5400		Some publications (DP)	Future	Future
		Some presentations (DP)	Future	Future

EMBSI Timeline

		Sep 00	Jan 01	Jan 02	Jan 03	Aug 03	Jan 04	Oct 04
EMBSI \$ Plan				212 K	718 K		1,213K	1,576K
\$ Actual				132 K	624 K		1,192K	1,533K
Project Mile-stones		Protocols approved Agreements with Fudan, CDC, IPHS		Lab & Studies Start Field testing, ME Pilots		Lab & Studies Start		
EMBSI Planned Work		Staffing, EA support materials, training		Troubleshoot, Monitor, Reviews				
	Protocols: write, review, approve	Design & oversight for EA - AML/NHL Study (2)						
		Questionnaire development						
EMBSI Actual Work		Staffing, EA support materials, training; (1)						
	Protocol write, review, approve	Design & oversight for EA - AML/NHL Study				Troubleshoot, Monitor, Reviews		
		JCML Database for EA (3)						
		Questionnaire development (4)				EMBSI reviews CDC lab & provides lab QA support(5)		

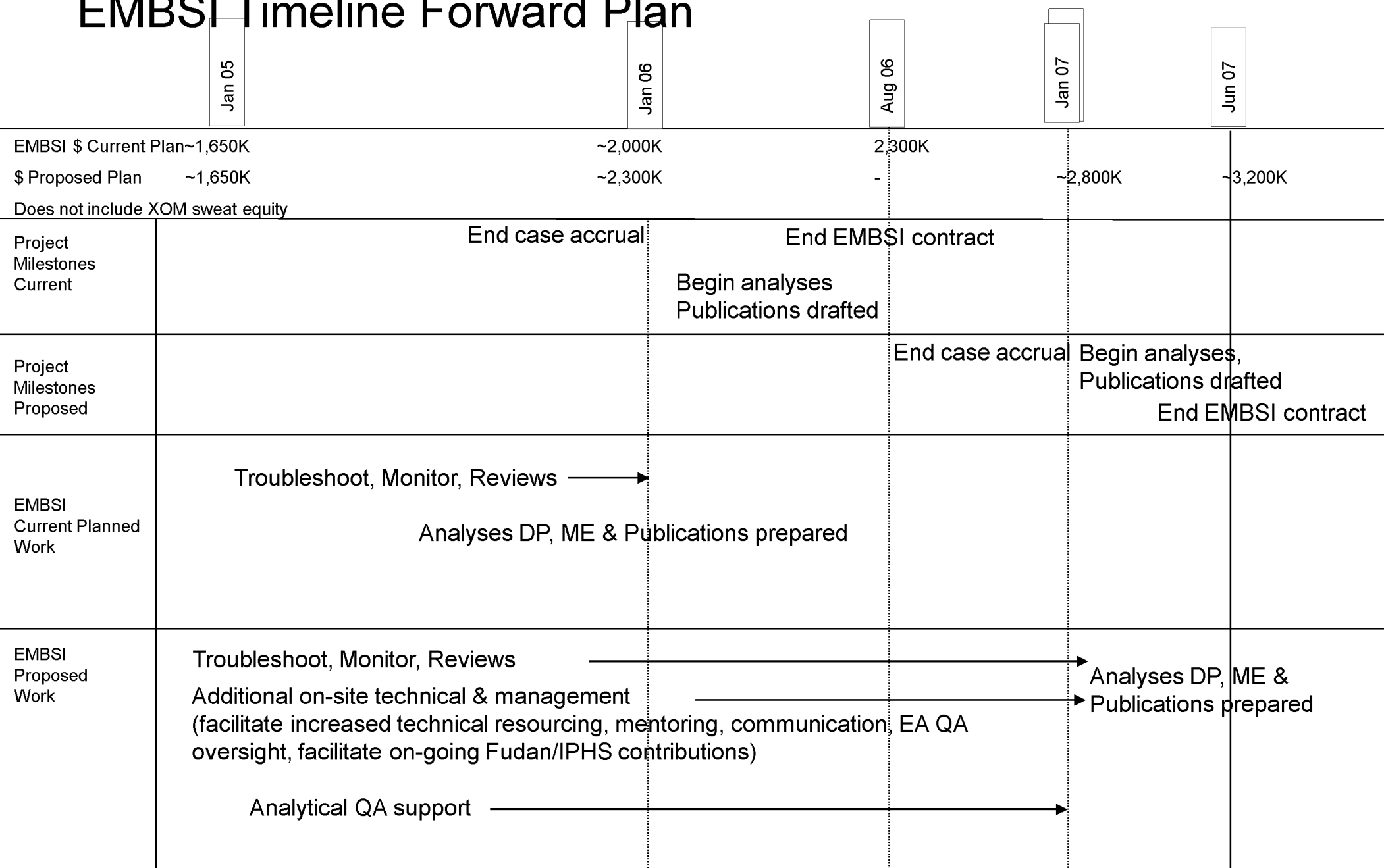
		Import delays (Chines regulation driven)	IPHS Role Change	EA crew to questionnaires
Comments		Agreements & revisions with Fudan, IPHS, CDC	Fudan recruiting EA	YZ begins support Turnover
			SARS	New IH Lab

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

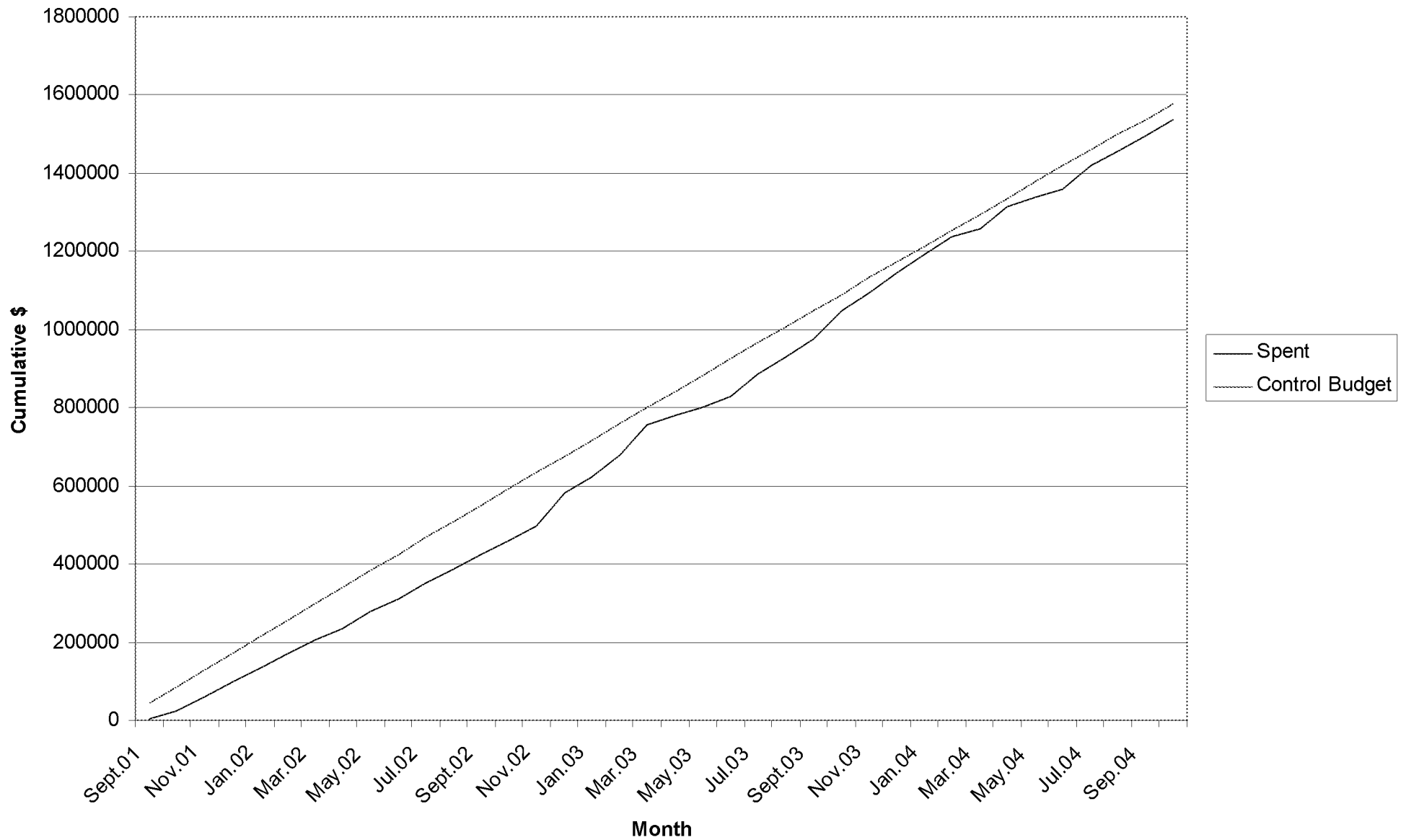
EA Reviews, EA Committee,
Local management issues

EMBSI Timeline Forward Plan



DRAFT

SHS EMBSI BUDGET



DRAFT

Exposure Assessment Options

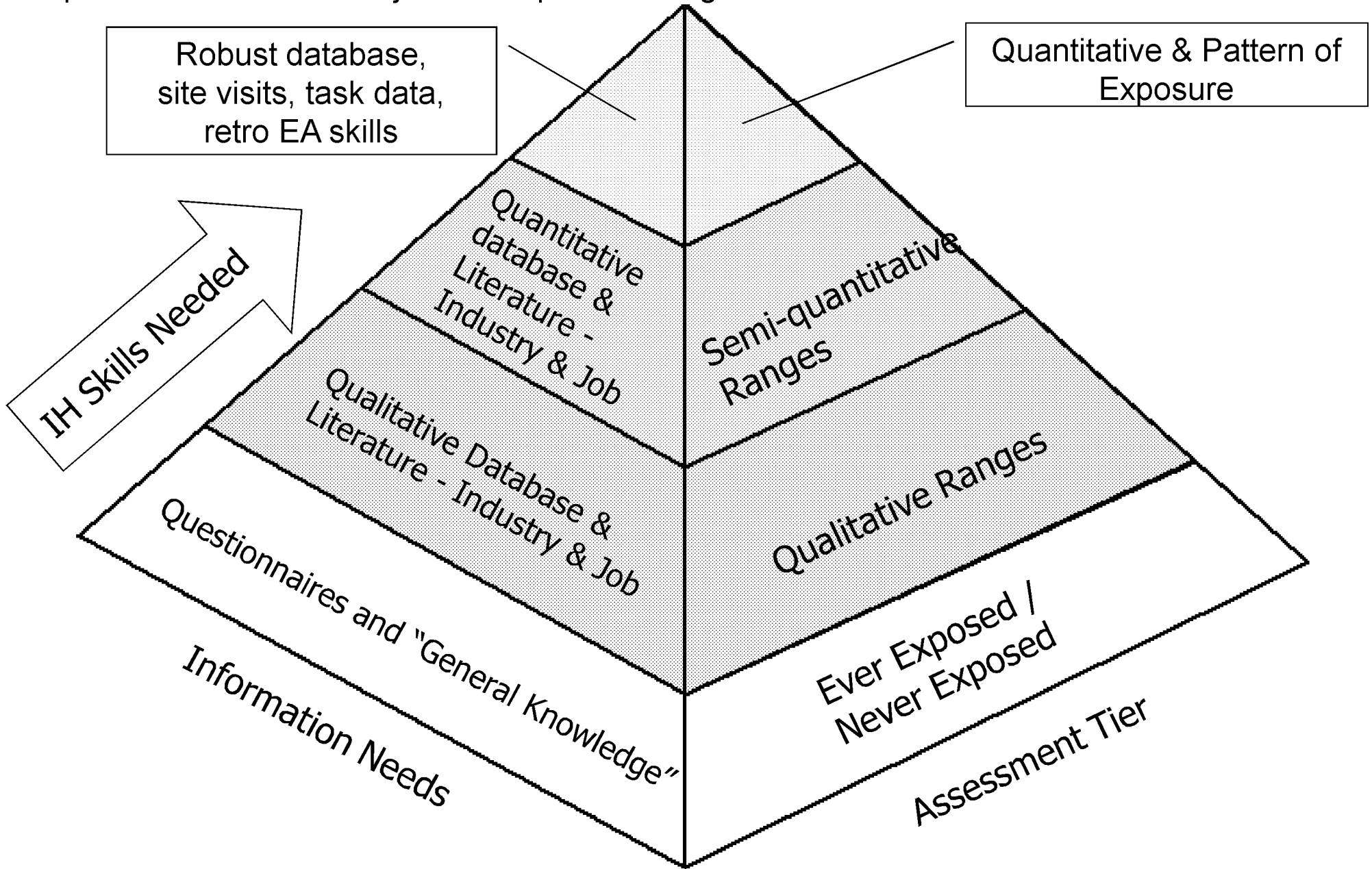
Review of strategies and study
impacts

Case Control Studies Tiered Design:

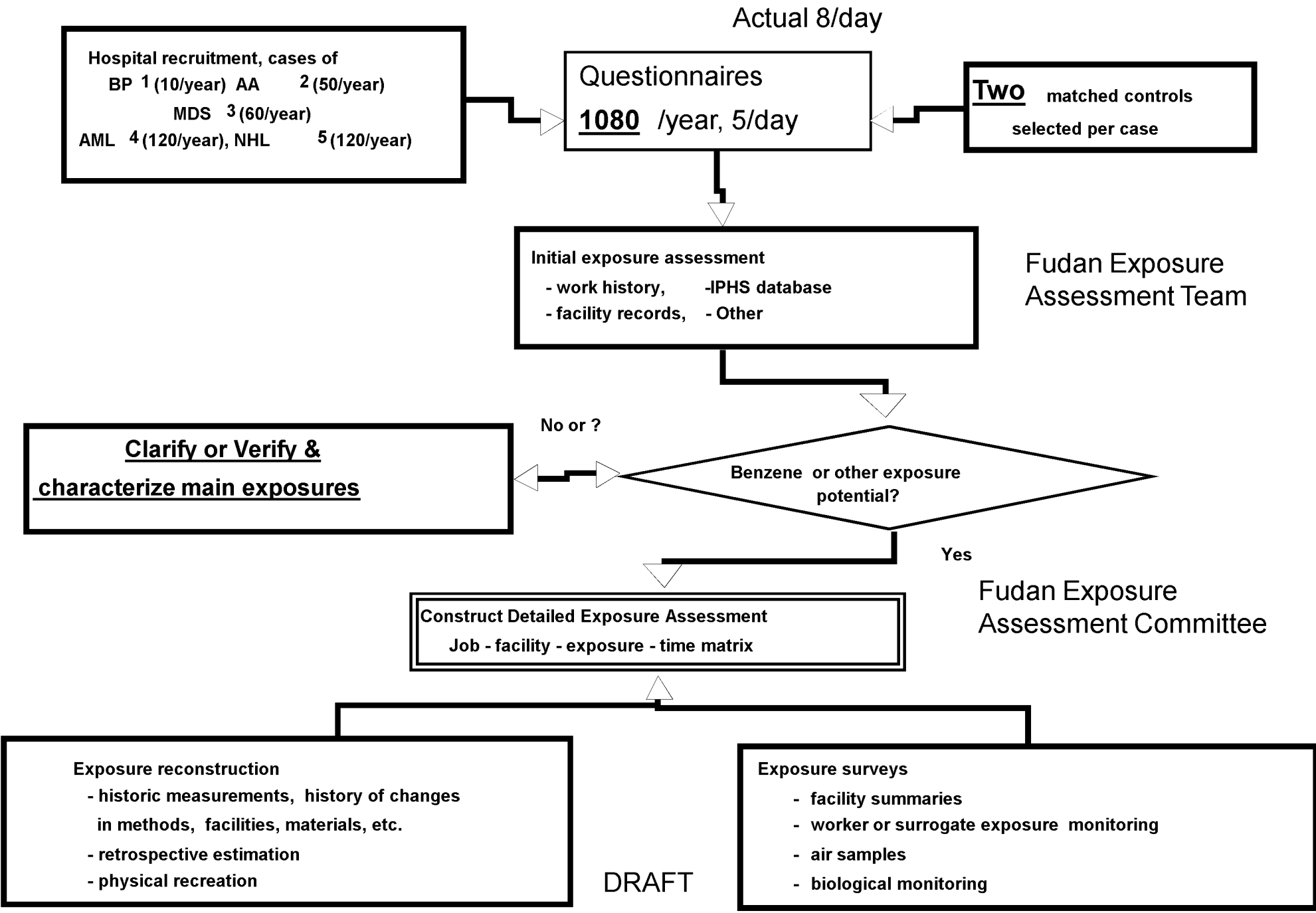
Expectation of Fewer Subjects Completed at Higher Tiers

Robust database,
site visits, task data,
retro EA skills

Quantitative & Pattern of
Exposure



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

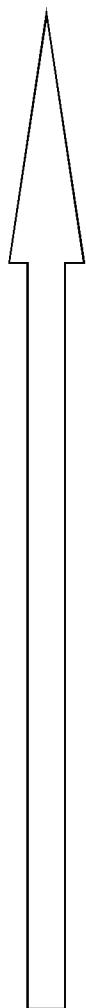
Note 2: “lower tiers” not planned or needed in the ME studies. Semi-quantitative ranks may be applied in some factories for Phase 1, but full quantitative assessment planned.

DRAFT

13

CC/DP Studies - Bz EA Impact Analysis

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



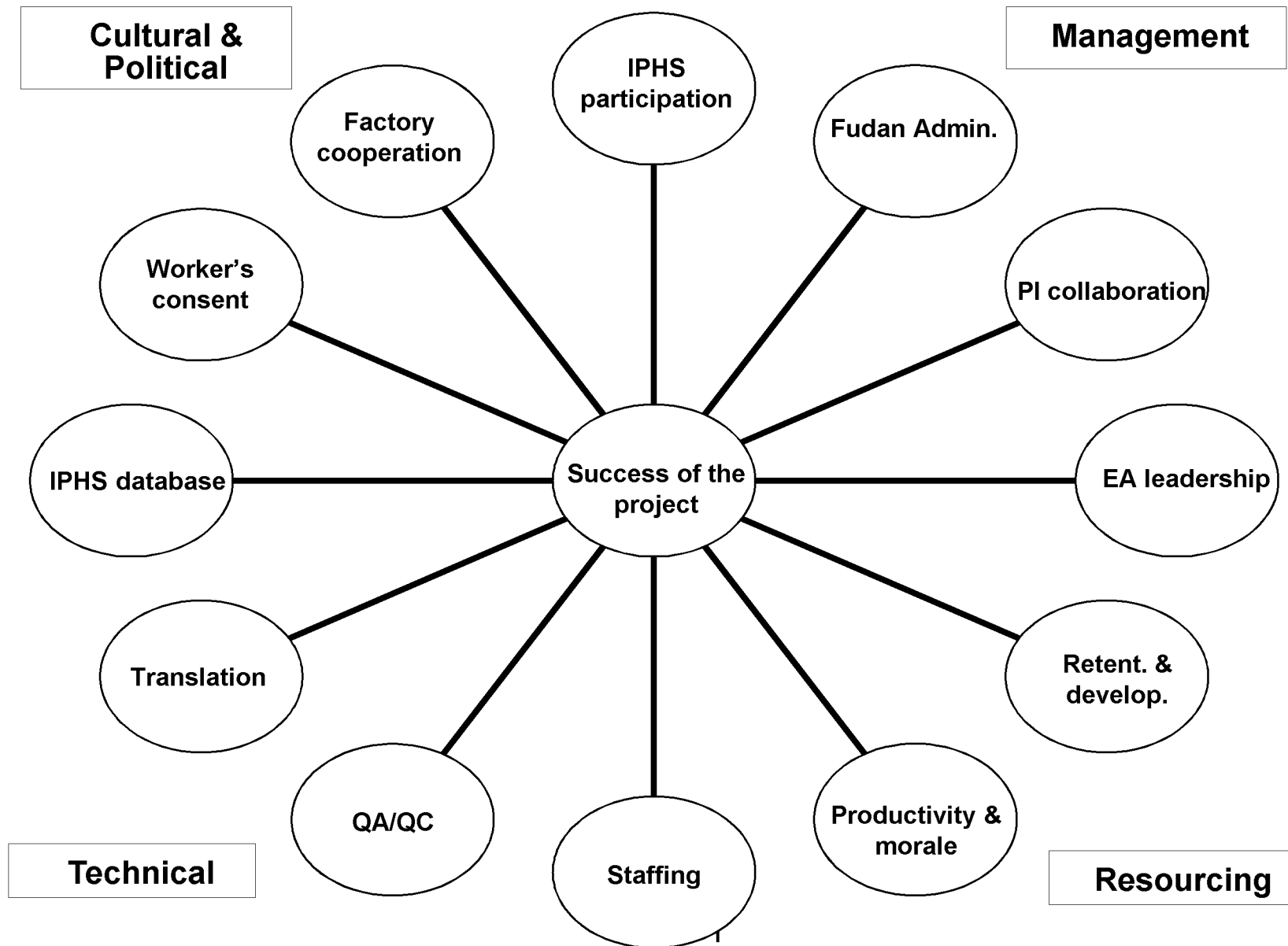
Read
Here to
Top

Go-forward Options

DRAFT

15

Many Factors Lead to Project Success



Opportunities

Action Item	Expected Benefits	Implementor	Enabler
#1 <i>YZ assignment to Shanghai and more EA support</i>	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 <i>Fund extension of the study</i>	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 <i>Re-engage IPHS</i>	More efficient factory selection, EA, more insight on IPHS database limitations	PI's	PA/Member Companies
#4 <i>Further support the Fudan team</i>	Continuous Improvement of PI collaboration, YZ effectiveness, post-study prob. of lab utilization	Oversight Committee	Technical/Oversight Committees
#5 <i>Perform independent QA/QC audits of Fudan IH laboratory and field (questionnaire EA) work</i>	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