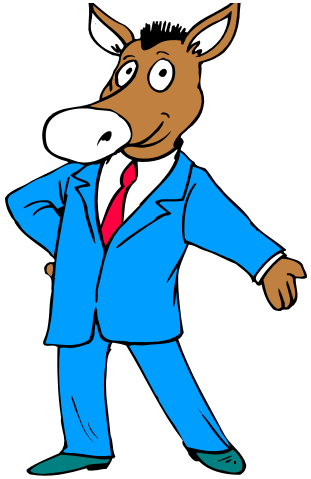

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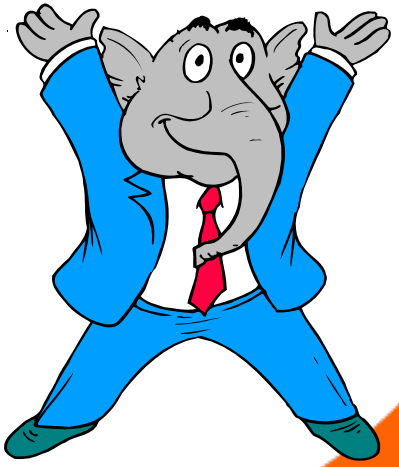
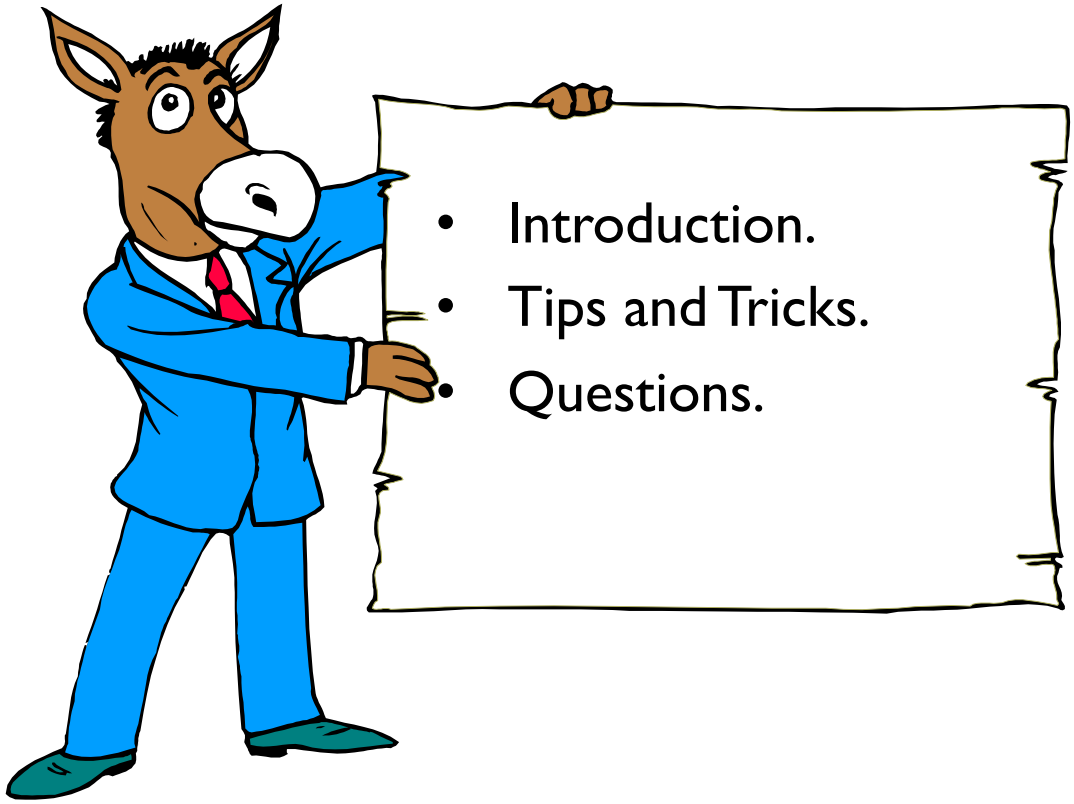
10 Tips to Make Friends with ADaM



Agenda



- Introduction.
- Tips and Tricks.
- Questions.

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Introduction

This presentation will provide perspective from a statistician at a CRO with years of experience in developing full CDISC compliant datasets for studies and submissions. Each item on the list is based on actual situations that we encountered. For each item, we will include helpful insight, including examples, logic and just plain good sense.

See what was done and hear recommendations on how to properly implement key aspects of the ADaM to improve traceability, quality and flexibility.

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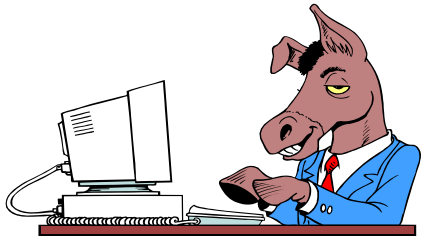
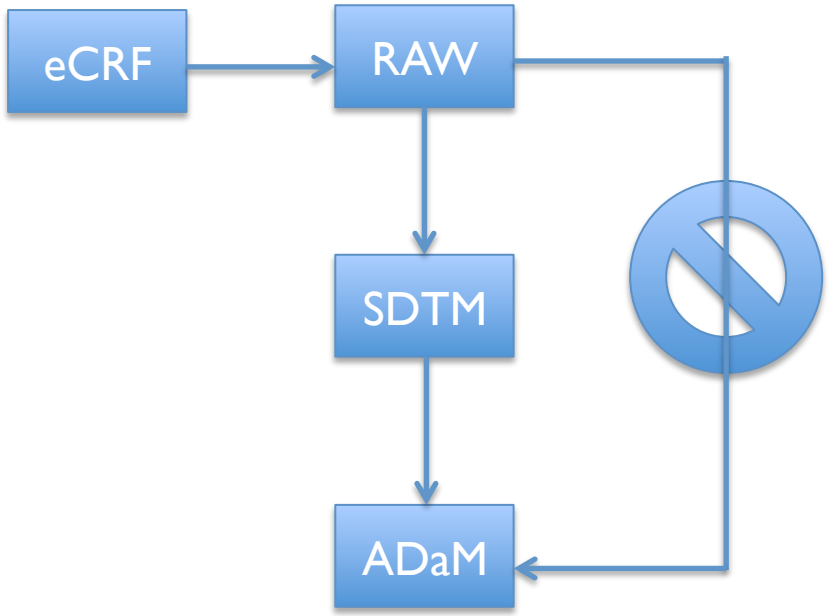
Tips and Tricks



1. Avoid the raw and input from SDTM

- Try not to develop any ADaM datasets from raw data.
- Skipping SDTM means any raw data used would have to be submitted to the regulatory agency (e.g., FDA).



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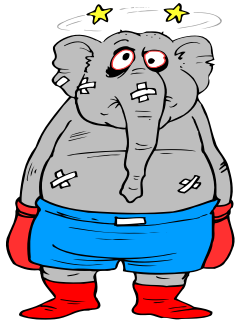
2. Analysis day (ADY) should be re-calculated when you don't have control of SDTM.

- It may be tempting to bring in your --DY variables directly from SDTM into ADY, but this can be dangerous.
- If your reference start date (RFSTDTC) and treatment start date (TRTSDTM) are inconsistent, this leads to differences between --DY and ADY, which can throw a wrench in your analyses.



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	RFSTDTC	TRTSDTM	LBDTC	LBDY_TRTSDTM	LBDY_RFSTDTC
1	25JAN2013	25JAN2013	15MAR2014	415	415
2	15FEB2013	15FEB2013	30APR2014	440	440
3	23MAR2013	24MAR2013	17MAY2014	420	421
4	17APR2013	17APR2013	15JUL2014	455	455

- Inconsistent dates can affect the Visit Windows.
- It's good practice to re-calculate study day based on treatment start date and assessment date.

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3. The importance of analysis visit (AVISIT) should not be overlooked

- Consult your statistician and ensure this is defined clearly in the SAP.

	B	D	E	J
1	Domain Name	Variable Name	Variable Label	Comment to be used in define.xml (Fill in if Origin is not CRF)
2	DOMAIN	VARNAME	VARLABEL	DEFCOMM
43	ADEG	AVISIT	Analysis Visit	if ABLFL = 'Y' then AVISIT = 'BASELINE' else if ADT < TRTEDT then AVISIT = 'WEEK n' (starting at Week 12) where ([(n-2)*7]-2) <= ADY <= ([n*7] + 4) if ADT = TRTEDT then AVISIT = 'END OF TREATMENT' Otherwise AVISIT=' '

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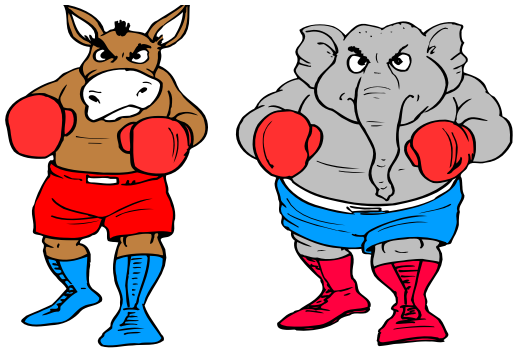
Continued…

- If visit windows are used, ensure they are continuous non-overlapping intervals and it is clear what to do if multiple visits occur within the same window.
- Don't forget about those unscheduled visits(included or not)!
- Your visit-based domains and results depend upon AVISIT.



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4. QC your ADaM specifications against your Finalized SAP

- Even though they are in a different format, they should "say" the same thing.
- Have a statistician perform a consistency check between both of these documents because any differences will lead to confusion and (possibly) errors.
- Start with identifying areas from the SAP/TLG shells that should be in ADaM, and start checking.
- SAP often updated during a trial and finalized before database lock.

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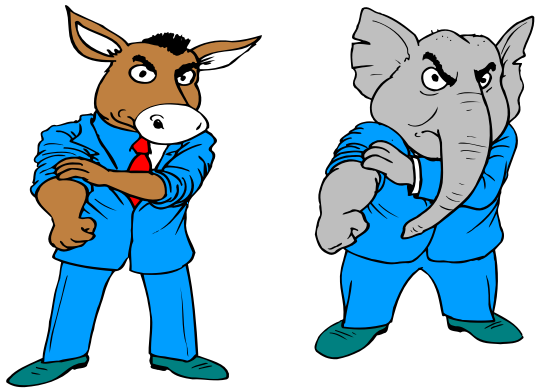

- From SAP

3.4 Safety Population

The safety population (SAF) will be used in the statistical analysis of safety. The SAF population includes all randomized patients who received at least one dose of study treatment. The SAF population will be used for all analyses of safety, and patients will be included in the treatment group based on treatment received.

- From Specs (case where they don't match)

SAFFL	Safety Population Flag	If DM.ARMCD in ('PBO') and DM.RFSTDTC is not missing, then SAFFL='Y'; Else SAFFL='N';

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5. Always triple check the important dates

- Items like randomization date and date of last dose in double-blind can be very critical.
- Treatment-emergent adverse event (TEAE) counts are based on these dates, so one incorrect date and your TEAE counts change (*fingers snapping)* "like that."
- Baseline is also dependent on these dates, so an error in these dates can lead to a different baseline value.
- Review all derived variable calculations (visit windows, efficacy calculations, change from baseline).

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6. Include all randomized subjects in your Basic Data Structure (BDS) domains

- It's tempting to only include subjects who received treatment (e.g., safety set) in your BDS domains. But the inevitable "oh no" may happen when the FDA requests that table that was originally run on the safety population to be run on ITT.
- If you don't put all ITT subjects in ADaM, you'll likely have to retrieve some from SDTM and then update ADaM to include them, and I suspect you'll want to avoid that.

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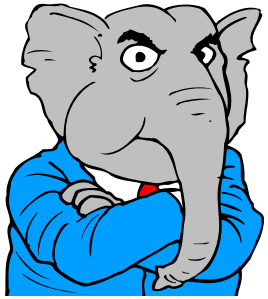
7. Include ALL levels of MedDRA and WHO Drug in ADAE (adverse events) and ADCM (concomitant medications)

- Don't just include SOC and PT, because you never know when your sponsor will want to review all levels of MedDRA coding.
- Before you know it, Lower Level Term is in your table shell and you do not want to have to get it from SDTM (SUPPAE, SUPPCM).



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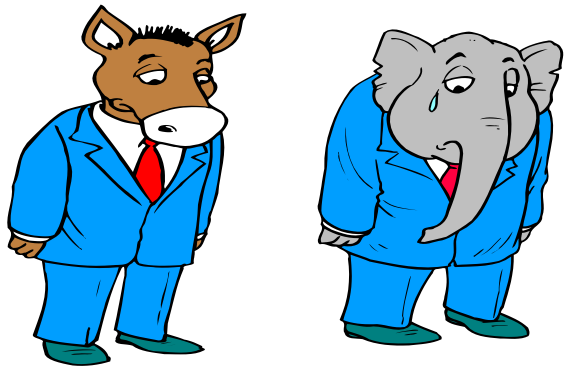
	AETERM	AEDECOD	SOC	PT	HLT	HLGT	LLT
1	VOMITING	Vomiting	Gastrointestinal disorders	Vomiting	Nausea and vomiting symptoms	Gastrointestinal signs and symptoms	Vomiting
2	UPPER RESPIRATORY INFECTION	Upper respiratory tract infection	Infections and infestations	Upper respiratory tract infection	Upper respiratory tract infections	Infections - pathogen unspecified	Upper respiratory infection
3	DIZZINESS UPON WAKING	Dizziness exertional	Nervous system disorders	Dizziness exertional	Neurological signs and symptoms NEC	Neurological disorders NEC	Dizziness exertional
4	MORNING DROWSINESS	Somnolence	Nervous system disorders	Somnolence	Disturbances in consciousness NEC	Neurological disorders NEC	Drowsiness
5	FALL	Fall	Injury, poisoning and procedural complications	Fall	Non-site specific injuries NEC	Injuries NEC	Fall



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8. Include a row for baseline

- Don't omit that baseline row just because you see the BASE variable
- The characteristics about the baseline record, such as date, are still going to be needed.
- Plus, the structure is useful for most PROC steps.

Variable Name	Variable Label	Type	Codelist / Controlled Terms	Core	CDISC Notes
BASE	Baseline Value	Num		Cond	Baseline analysis value. Required if dataset supports analysis or review of baseline value or functions of baseline value. A baseline record may be derived (e.g., it may be an average) in which case DTYPE must also be populated. If BASE is populated for a parameter, and BASE is non-null for a subject for that parameter, then there must be a record flagged by ABLFL for that subject and parameter.

Variable Name	Variable Label	Type	Codelist / Controlled Terms	Core	CDISC Notes
ABLFL	Baseline Record Flag	Char	Y	Cond	Character indicator to identify the baseline record for each parameter, or if there is more than one baseline definition, for each parameter and baseline type (BASETYPE). See BASETYPE in Table 3.2.4.1. ABLFL is required if BASE is present in the dataset. A baseline record may be derived (e.g., it may be an average), in which case DTYPE must also be populated. If BASE is populated for a parameter, and BASE is non-null for a subject for that parameter, then there must be a record flagged by ABLFL for that subject and parameter.

Domain Abbreviation	Parameter	Analysis Visit	Baseline Flag	Analysis Relative Day	Analysis Value	Baseline Value	Change from Baseline
ADEG	Heart Rate	BASELINE	Y	-2	60	60	.
ADEG	Heart Rate	WEEK 12		78	56	60	-4.00
ADEG	Heart Rate	WEEK 24		162	64	60	4.00
ADEG	Heart Rate	WEEK 36		246	73	60	13.00

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9. Know the contents (populations, records) that are included in each ADaM dataset

- For example, does ADAE include only TEAEs or non-TEAEs as well? How about double-blind vs. open-label AEs?

	DOMAIN	APERIODC	AETERM	AEDECOD	TEAEFL
96	ADAE	Open-label Titration	Worsening	Oedema	Y
97	ADAE		Worsening	Oedema Pe	
98	ADAE	Open-label Titration	Worsening	Oedema Pe	Y
99	ADAE	Double-blind	Diarrhea	Diarrhoea	Y
100	ADAE	Double-blind	Nausea	Nausea	Y
101	ADAE	Double-blind	Rhinorrhe	Rhinorrho	Y
102	ADAE	Double-blind	Vomiting	Vomiting	Y
103	ADAE	Long-term	Acute Dia	Diarrhoea	Y

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- What populations are included in ADVS (vital signs), ADEG (ECGs) and ADLB (labs)? All randomized or only those receive study drug?

	Domain Abbreviation	Safety Population Flag	Controlled Study Flag	Uncontrolled Study Flag	Safety Set Flag	Double-blind Safety Set Flag	Long-term Safety Set Flag	Date of First Exposure to Treatment	Date of Last Exposure to Treatment	Date of Randomization	Visit Name
1	ADEG	Y	Y	N	Y	Y	N	08APR2013	13AUG2013	21MAY2013	VISIT 19 RAND/BASELINE
2	ADEG	Y	Y	N	Y	Y	N	30JUL2013	11DEC2013	18SEP2013	VISIT 19 RAND/BASELINE
3	ADEG	Y	Y	N	Y	Y	N	08AUG2013	18DEC2013	25SEP2013	VISIT 19 RAND/BASELINE
4	ADEG	Y	Y	N	Y	Y	N	06SEP2013	13JAN2014	21OCT2013	VISIT 19 RAND/BASELINE
5	ADEG	Y	Y	N	Y	Y	N	28AUG2013	31OCT2013	25OCT2013	VISIT 19 RAND/BASELINE
6	ADEG	Y	Y	N	Y	Y	N	09SEP2013	14JAN2014	22OCT2013	VISIT 19 RAND/BASELINE
7	ADEG	Y	Y	N	Y	Y	N	08NOV2013	10MAR2014	16DEC2013	VISIT 19 RAND/BASELINE
8	ADEG	Y	Y	N	Y	Y	N	02JAN2014	04MAY2014	11FEB2014	VISIT 19 RAND/BASELINE
9	ADEG	Y	Y	N	Y	Y	N	31DEC2012	29APR2013	07FEB2013	VISIT 19 RAND/BASELINE
10	ADEG	Y	Y	N	Y	Y	N	19DEC2012	02APR2013	10JAN2013	VISIT 19 RAND/BASELINE

- When Integrating, knowing your analysis dataset will help clarify potential CRF differences.

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10. Invest your time here

- Let's face it, ADaM programming takes a long time.
- This is where your populations, derivations, imputations and calculations reside.
- So time spent here is value-added, and can dramatically save time for your TLG programming.
  - Adding a Analysis dataset to make TLG programming easier.

ADVPS	VSPCS01	PCS Chg in SBP & PR from Base	If CHG>= 10 with VSTESTCD = 'SYSBP' and CHG>= 5 with VSTESTCD = 'PULSE', then VSPCS01 = 'Y'; Else if CHG is not missing with VSTESTCD = 'SYSBP' and CHG is not missing with VSTESTCD = 'PULSE', then VSPCS01 = 'N';

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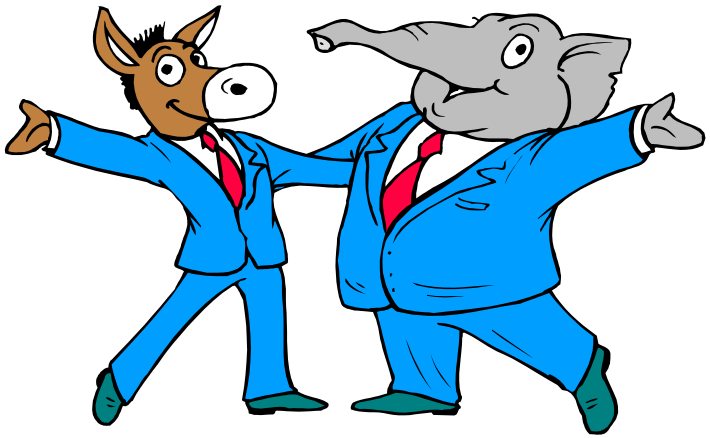
Table 5: Vital Signs PCS Criteria

Vital Signs Parameter	Increases	Decreases
SBP	> 180 mmHg AND ≥ 20 mmHg increase from Baseline	<= 90 mmHg AND >= 20 mmHg decrease from Baseline
DBP	≥ 105 mmHg AND ≥ 15 mmHg increase from Baseline	<= 50 mmHg AND >= 15 mmHg decrease from Baseline
Pulse Rate	≥ 120 bpm AND ≥ 15 bpm increase from Baseline	<= 50 bpm AND >= 15 bpm decrease from Baseline
SBP and Pulse Rate	Increase from Baseline of ≥ 10 mmHg for SBP and ≥ 5 bpm for Pulse Rate	N/A
DBP and Pulse Rate	Increase from Baseline of ≥ 5 mmHg for DBP and ≥ 5 bpm for Pulse Rate	N/A



ADVS

Domain Abbreviation	Visit Name	Parameter Code	Baseline Record Flag	Analysis Value	Analysis Value (C)	Baseline Value	Change from Baseline
ADVS	SCREENING	PULSE		79	79	.	.
ADVS	BASELINE	PULSE	Y	59	59	59	.
ADVS	VISIT 2	PULSE		62	62	59	3
ADVS	VISIT 3	PULSE		68	68	59	9
ADVS	VISIT 4	PULSE		64	64	59	5
ADVS	VISIT 5	PULSE		67	67	59	8
ADVS	VISIT 6	PULSE		69	69	59	10
ADVS	VISIT 7	PULSE		62	62	59	3
ADVS	SCREENING	SYSBP		134	134	.	.
ADVS	BASELINE	SYSBP	Y	121	121	121	.
ADVS	VISIT 2	SYSBP		126	126	121	5
ADVS	VISIT 3	SYSBP		107	107	121	-14
ADVS	VISIT 4	SYSBP		96	96	121	-25
ADVS	VISIT 5	SYSBP		150	150	121	29
ADVS	VISIT 6	SYSBP		120	120	121	-1
ADVS	VISIT 7	SYSBP		130	130	121	9

ADVPS

Domain Abbreviation	Visit Name	PCS Chg in SBP & PR from Base
ADVPS	SCREENING	
ADVPS	BASELINE	
ADVPS	VISIT 2	N
ADVPS	VISIT 3	N
ADVPS	VISIT 4	N
ADVPS	VISIT 5	Y
ADVPS	VISIT 6	N
ADVPS	VISIT 7	N

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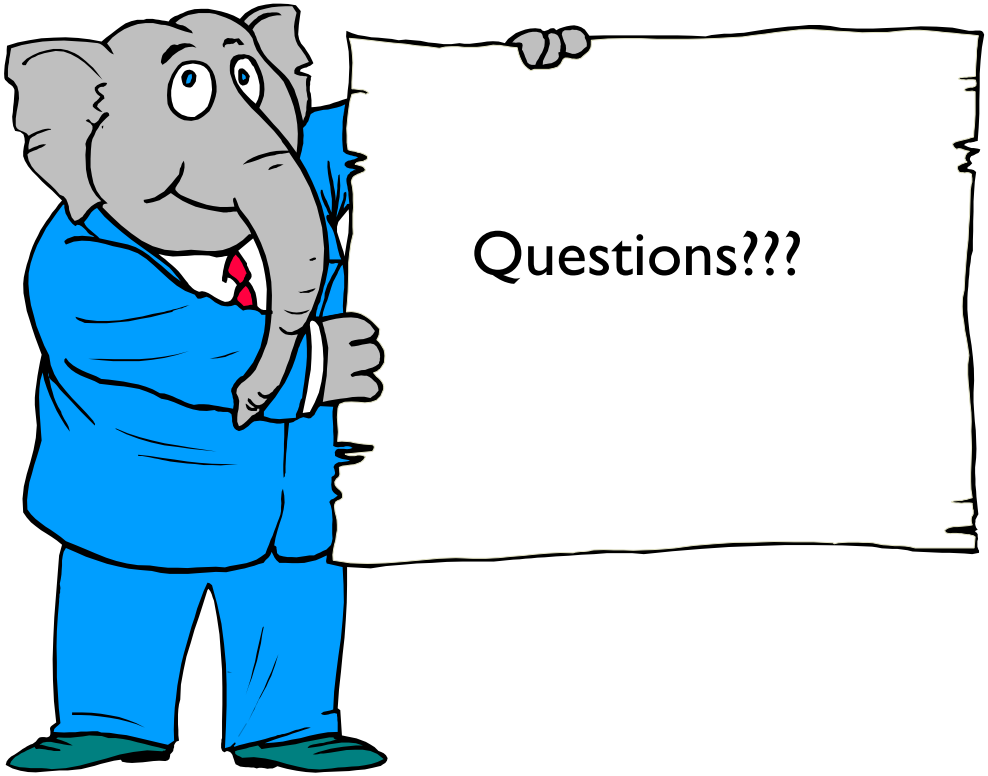

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