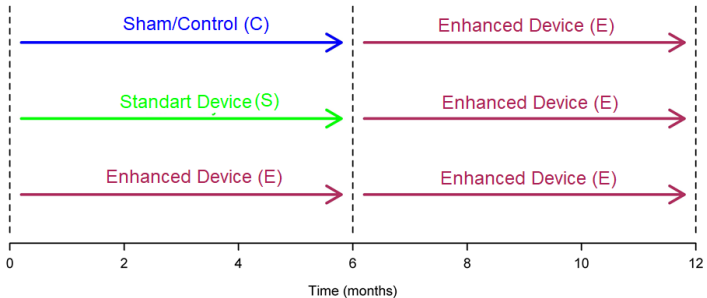



### Requested comparisons

- C months 0-6 vs S months 0-6
- C months 0-6 vs E months 0-6
- S months 0-6 vs E months 0-6
- C months 0-6 vs E months 6-12
- S months 0-6 vs E months 6-12
- ~~E months 0-6 vs E months 6-12 (why?)~~



Time (months)

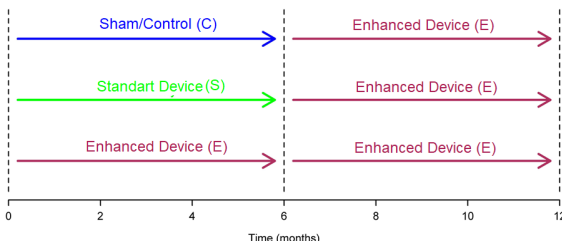
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### Sample size preliminaries



- Primary analysis:
  - Compares months 0-6 to months 0-12 for C and S arms?
  - Or: compare months 0-6 between arms?
- Change from baseline of baseline adjusted?

Note: Decision was BL adjusted analysis in order to avoid Lord's paradox

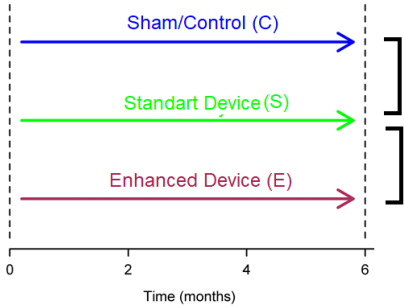


Time (months)

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  **Primary analyses**

- C months 0-6 vs S months 0-6
- S months 0-6 vs E months 0-6




Time (months)

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  **Assumptions**

1. Distribution of HbA1c – assuming normal distribution
2. Effect size: Mean of HbA1c at months 0 and 6 for each group
3. Variation: SD of HbA1c at months 0 and 6 for each group
4. Correlation between HbA1c measures that are 6 months apart
5. Noise of effect


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## Multiplicity issues

- Co-primary
  - Test both hypotheses simultaneously at overall significance level  $\alpha$
- Hierarchy:
  - Test first hypothesis at significance level  $\alpha$ 
    - If first hypothesis is rejected then test second hypothesis at significance level  $\alpha$
    - Else: second hypothesis is not rejected

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## Simulation of single study

```
# assumption
group_size=100
base_a1c=8.25
sd_a1c=0.5
effect_B=-0.2
effect_C=-0.6
r=0.6
sd_noise=0.02

# start with 3*group_size subjects
# for each of them simulate a1c at month 0 and month 6, assuming no effect
# covariance matrix of a1c measures at months 0 and 6
var_a1c=sd_a1c^2
covmat=matrix(c(var_a1c, r*var_a1c, r*var_a1c, var_a1c), nrow=2)
pats=mvrnorm(n=3*group_size, mu=rep(base_a1c,2), sigma=covmat)
pats=as.data.frame(pats)
names(pats)=c("month0", "month6")
pats$study_group=""
```

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## Simulation of single study

```


# set study groups and effects
range=1:group_size
pats$study_group[range]="A" # control group, no effect, except noise
pats$month6[range]=pats$month6[range]+rnorm(group_size, mean=0, sd=sd_noise)

# group B
range=(group_size+1):(2*group_size)
pats$study_group[range]="B"
pats$month6[range]=pats$month6[range]+rnorm(group_size, mean=effect_B, sd=sd_noise)

# sensors+model group with specified effect
range=(2*group_size+1):(3*group_size)
pats$study_group[range]="C" # sensors+model group, effect=effect!
pats$month6[range]=pats$month6[range]+rnorm(group_size, mean=effect_C, sd=sd_noise)

```

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## Analysis of simulated study

```

# ancova + ci
model=lm(month6 ~ month0 + study_group, data=pats)
model_emeans=emmeans(model, "study_group")
model_contrast=contrast(model_emeans,
                        list("AB" = c(1, -1, 0),
                             "AC" = c(1, 0, -1)))
model_contrast=as.data.frame(model_contrast)

> model_emeans
  study_group emmean    SE df lower.CL upper.CL
A           8.34 0.0399 296    8.26    8.42
B           8.11 0.0399 296    8.04    8.19
C           7.66 0.0399 296    7.58    7.74

Confidence level used: 0.95
> model_contrast
  contrast estimate      SE df  t.ratio    p.value
1      AB 0.2258135 0.05641718 296  4.002566 7.926214e-05
2      AC 0.6786655 0.05635753 296 12.042145 1.891710e-27
.

```

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## Testing the hypotheses

```
# parallel testing
adjusted_pvalues=p.adjust(p=model_contrast$p.value, method="hochberg")
reject1=as.numeric(adjusted_pvalues[1]<0.05)
reject2=as.numeric(adjusted_pvalues[2]<0.05)

# hierarchical testing
if(model_contrast$p.value[1]>0.05){
  reject1=0
  reject2=0
} else {
  reject1=1
  if(model_contrast$p.value[2]>0.05){
    reject2=0
  } else {
    reject2=1
  }
}
```