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6 December 2010

Integrity Check for the Interstitial Cystitis Clinical Trials Group (ICCTG) Pentosan Polysulfate and Oral Hydroxyzine (PPS Hydroxyzine) Study-RCT#1

As a partial check of the integrity of the ICCTG RCT#1 dataset archived in the NIDDK data repository, a set of tabulations was performed to verify that published results can be reproduced using the archived dataset. Analyses were performed to duplicate selected results for the data published by Sant et al [1] in the *Journal of Urology* in September 2003. The results of this dataset integrity check (DSIC) are described below. The full text of the *Journal of Urology* article can be found in Attachment 1, and the STATA code for our tabulations is included in Attachment 2.

The intent of this DSIC is to provide confidence that the data distributed by the NIDDK repository is a true copy of the study data. Our intent is ***not*** to assess the integrity of the statistical analyses reported by study investigators. As with all statistical analyses of complex datasets, complete replication of a set of statistical results should not be expected on a first (or second) exercise in secondary analysis. This occurs for a number of reasons including differences in the handling of missing data, restrictions on cases included in samples for a particular analysis, software coding used to define complex variables, etc. Experience suggests that most discrepancies can ordinarily be resolved by consultation with the study data coordinating center (DCC), however this process is labor-intensive for both DCC and Repository staff. It is thus not our policy to resolve every discrepancy that is observed in an integrity check. Specifically, we do not attempt to resolve minor or inconsequential discrepancies with published results or discrepancies that involve complex analyses, *unless NIDDK Repository staff suspect that the observed discrepancy suggests that the dataset may have been corrupted in storage, transmission, or processing by repository staff*. We do, however, document in footnotes to the integrity check those instances in which our secondary analyses produced results that were not fully consistent with those reported in the target publication.

Background. The Interstitial Cystitis Clinical Trials Group (ICCTG) RCT#1 trial was a pilot clinical trial using a 2x2 factorial study design with double masked drug treatment to evaluate the feasibility of oral pentosan polysulfate (PPS) and oral hydroxyzine in patients with interstitial cystitis (IC) in a larger comparative trial.

A total of 121 participants were randomized over 18 months and followed for 24 weeks. The primary endpoint was a patient reported global response assessment (GRA) of overall symptoms. Secondary endpoints included symptom indexes and patient reports of urinary pain, urgency, and frequency. The paper by Sant et al. provides the main study results for the pilot trial.

In this DSIC, we compared our results to the published results in Table 2 (Baseline patient characteristics by treatment group), Table 3 (Changes in symptoms from baseline to 24 weeks by main comparisons) and Table 4 (Changes in symptoms from baseline to 24 weeks by individual treatment arm). The percentages of patients with complete secondary end point data, by main comparisons and individual treatment arms, were not checked (see below).

The tables in this DSIC reproduce very closely the results presented in Tables 2 through 4.

Baseline Patient Characteristics by Treatment Group. Table A lists the datasets, data forms, data variables, and algorithms for derived analysis variables that we used in our replication for Table 2 of Sant et al. The dataset “icctgrct1” is an analysis file provided by the DCC along with the form-based files. For this dataset the forms upon which the analysis variables are based are shown in parentheses. We did not use the original form-based variables – rather we used the variables as contained in icctgrct1, the analysis file. We note that the analysis dataset does not include the variable ‘number of prior symptoms 52 or more weeks’. This variable, bsym1_04, can be found in the baseline data, BSYM1_PKT.sas7bdat. By

merging this dataset with the analysis dataset using subject and ccid, it is possible to obtain the results in the published manuscript. We also note that based on the maximum possible value of 42 for the Wisconsin IC Symptom Survey, we determined that only 7 of the 25 items on the Wisconsin Symptom Survey were included (with a maximum value of 6), so we identified those that were related to interstitial cystitis, as shown in Table A.

The published results and the DSIC results are shown in Table B.

Changes in Symptoms from Baseline to 24 Weeks by Main Comparisons and by Treatment Group. Table C lists the datasets, data forms, data variables, and algorithms for derived analysis variables that we used in our replication of Tables 3 and 4 of Sant et al. Tables D and E contain the published results and the DSIC results, by main comparisons and individual treatment arms, respectively. Values shown in **bold** do not match (within rounding at the 0.1 level) the published values.

Primary outcome. The primary endpoint was a participant reported global response assessment at 24 weeks relative to overall baseline symptoms. A 7-point centered scale was used and included markedly worse, moderately worse, slightly worse, no change, slightly improved, moderately improved, and markedly improved. Participants who reported either of the last two categories were defined as treatment responders. The DSIC results agree with the published results.

Secondary outcomes. The remainder of Tables D and E consider the changes in secondary outcomes from baseline to week 24. The first sentence of the footnote (**) states - "Mean values for the analysis of secondary outcomes were based on only those subjects who had complete data for all points, excluding withdrawals and those with missing data." This seemed to be open to alternative interpretations, since the data come from several different forms:

- Pain score and urgency score come from the FUSYM (Follow-Up Symptoms) form and from the BSYM1 (Baseline symptoms, Baseline 1 visit) and BSYM2 (Baseline symptoms, baseline 2 visit) files for the baseline.
- IC Symptom Index and Problem Index come from the SYMPROB (IC Symptom Index and Problem Index) form.
- Wisconsin IC Symptom Inventory is derived from the UNIVWIS form.

Furthermore, these forms are not all collected at the same time points. For this DSIC, these tabulations were not reproduced.

Summary. Descriptive results provided by this DSIC for the baseline measurements and the primary and secondary outcomes closely agree with published values.

Table A. Datasets, forms, variables, and analysis variable algorithms for Sant et al (2003) Table 1.

	Analysis Dataset Variable(s)	Data form(s)	Data variable(s)	Algorithm (Analysis)
No.randomized	Treatment	Form not provided to repository		
No. female (%)	Gender	(DEMO)	GENDER	If gender==0
No. race (%):	Race	(DEMO)	RACE	Recode race (5=1) (1 4 6 7=4)
White Black Hispanic Other				
No. prior symptoms 52 or more wks (%)	Bsym1_04*	(BSYM1)	PAIN1, FREQ1,URGENCY1, DUR1	
Mean age ± SD	Age	(DEMO)	AGE	Age at randomization
Mean pain score ± SD (0–9) **	Pain1, pain2	(BSYM1)	PAIN1, PAIN2,	Pain_x = (pain1+pain2)/2
Mean urgency score ± SD (0–9)**	Urgency1, urgency2, Avg_urg	(BSYM2)	URGENCY1, URGENCY2	Urgency_x = (urgency_1 +urgency_2)/2
Mean 24-hr frequency ± SD**	Freq1, freq2, Avg_freq	(BSYM2)	FREQ1,FREQ2	Freq_x=(freq1+freq2)/2
Mean IC Symptom Index (0–20) ± SD	Icindexsym_24wk, Icindexsym_chgbase24wk	(SYMPROB)	SYM_Q1-SYMQ4, SYM_SCOR	ICSYMP_BASE=icindexsym_24wk-Icindexsym_chgbase24wk
Mean IC Problem Index (0–16) ± SD	Icindexpro_24w, Icindexpro_chgbase24wk	(SYMPROB)	PROB_Q1-PROB_Q4, PROB_SCO	ICPRO_BASE=icindexpro_24wk-Icindexpro_chgbase24wk
Mean Wisconsin IC Score (0–42) ± SD	Wiscbase	(UNIVWISC)	Univwis_, univwis0, univwis8, univwi16, univwi19, univwi21, univwi23 (symptoms 1,2,10,18, 21,23,25)	

* Variable not included in analysis dataset. Result matching published data can be obtained by merging BSYM1_PKT.sas7bdat with icctgrct1.sas7bdat by subj and ccid.
** Average of 2 baseline scores

Table B. DSIC results for Table 2 of Sant et al (2003), "Baseline patient characteristics by treatment group".

	Placebo			Hydroxyzine Alone		
	Published	DSIC		Published	DSIC	
	Mean ± SD or n (%)	N %	Mean, SD	Mean ± SD or n (%)	N %	Mean, SD
No. randomized	31	31		31	31	
No. female (%)	28 (90)	28(90)		26 (84)	26(84)	
No. race (%):						
White	29 (34)	29 (34)		26(84)	26(84)	
Black	0	0		2(6)	2(6)	
Hispanic	0	0		2(6)	2(6)	
Other	2(6)	2(6)		1(3)	1(3)	
No. prior symptoms 52 or more wks (%)	29 (94)			30(97)		
Mean age ± SD	41.6 ± 15.5		41.6 ± 15.5	47.8±13.9		47.8±13.9
Mean pain score ± SD (0–9)†	6±1.3		6±1.3	6±1.0		6±1.0
Mean urgency score ± SD (0–9)†	6.5±1.5		6.5±1.5	6.7±1.4		6.7±1.4
Mean 24-hr frequency ± SD	18.9±10.3		18.9±10.3	19.9±6.3		19.9±6.3
Mean IC Symptom Index ± SD (0-20)	14.6±3.3		**14.5±3.5**	14.1±3.7		**13.6±3.8**
Mean IC Problem Index ± SD (0-16)	12.8±2.4		**12.8±2.5**	12.9±2.9		**12.8±3.1**
Mean Wisconsin IC Symptom Inventory ± SD (0-42)	32.9±6.7		32.9±6.7	32.3±7.8		32.3±7.8

† Average of 2 baseline scores.

Table B. DSIC results for Table 2 of Sant et al (2003), "Baseline patient characteristics by treatment group" (continued).

	PPS Alone			Combination therapy		
	Published	DSIC		Published	DSIC	
	Mean ± SD or n (%)	N %	Mean, SD	Mean ± SD or n (%)	N %	Mean, SD
No. randomized	29	29		30	30	
No. female (%)	26(90)	26(90)		28(93)	28(93)	
No. race (%):						
White	21 (72)	21 (72)		26(87)	26(87)	
Black	4(14)	4(14)		2(7)	2(7)	
Hispanic	3910)	3910)		1(3)	1(3)	
Other	1(4)	1(4)		1(4)	1(4)	
No. prior symptoms 52 or more wks (%)	29(96)			27(90)		
Mean age ± SD	48.7±15.1		48.7±15.1	43.7±15.1		43.7±15.1
Mean pain score ± SD (0–9)†	6.3±1.4		6.3±1.4	5.8±1.1		5.8±1.1
Mean urgency score ± SD (0–9)†	6.9±1.2		6.9±1.2	6.1±1.4		6.1±1.4
Mean 24-hr frequency ± SD	18.3±6.8		18.3±6.8	16.5±8		16.5±8
Mean IC Symptom Index ± SD (0-20)	14.3±3.3		**14.4±3.5**	13.3±3.5		**14±3**
Mean IC Problem Index ± SD (0-16)	12.8±2.7		**12.8±2.8**	11.8±2.5		**12±2**
Mean Wisconsin IC Symptom Inventory ± SD (0-42)	30.4±6.8		30.4±6.8	28.4±8.5*		28.4±8.5*

*A subject on the combination therapy was missing baseline UW IC score data.

† Average of 2 baseline scores.

Table C. Datasets, forms, variables, and analysis variable algorithms for Sant et al (2003) Tables 3 and 4.

	Analysis Dataset Variable	Data form(s)	Data variable(s)	Algorithm (Analysis)
No. subjects randomized	Treatment	Form not provided to repository		
No. responders (%):	Globresp, resp	(PTCLOSE)	PTCLOSE_	ptclose_=6,7
No. complete secondary end point data*	--	--	--	--
Mean pain score ± SD (0–9)†	Pain_chgbase24wk	(BSYM1,BSYM2, FUSYMP)	PAIN1, PAIN2, FUSYM_01	Xpain=fusym01-((pain1+pain2)/2)
Mean urgency score ± SD (0–9)	Urgency_chgbase24wk	(BSYM1,BSYM2, FUSYMP)	URGENCY1, URGENCY2,FUSYM_02	Xurgency=fusym_02-((urgency1+urgency2)/2)
Mean 24-hr frequency ± SD	Voidfreq_chgbase24wk	(BSYM1,BSYM2, FUSYMP)	FREQ1, FREQ2, FUSYM_03	Xfreq=fusym_03-(freq1+freq2)/2)
Mean IC Symptom Index ± SD (0-20)	Icindexsym_chgbase24wk	(SYMPROB)	SYM_SCOR	Sum(sym_Q1, sym_Q2, sym_Q3, sym_Q4)/4
Mean IC Problem Index ± SD (0-16)	Icindexpro_chgbase24wk	(SYMPROB)	PROB_SCO	Sum (prob_Q1, prob_Q2, prob_Q3, prob_Q4)/4
Mean Wisconsin IC Score ± SD (0-42)	Wisc_chgbase24wk	(UNIVWIS)	Univwis_, univwis0, univwis8, univwi16, Univwi19, univwi21, univwi23 (symptoms 1,2,10,18, 21,23,25)	

* Results were not tabulated due to various different interpretations of cases with complete data at baseline and 24 weeks. Also, no adjustment was made for multiple comparisons.

TABLE D. DSIC results from Sant et al (2003) Table 3. Changes in symptoms from baseline to 24 weeks by main comparison.

	Hydroxyzine						PPS					
	Placebo			Drug			Placebo			Drug		
	Published	DSIC N	DSIC:Mean SD or %	Published	DSIC N	DSIC:Mean SD or %	Published	DSIC N	DSIC:Mean SD or %	Published	DSIC N	DSIC: Mean SD or %
No. subjects randomized	60		60	61		61	62		62	59		59
No. responders (%):	12(20)		12(20)	19(31)		19(31)	11(18)		11(18)	20(34)		20(34)
No.complete secondary endpoint data (%)*												
Mean pain score ± SD (0-9)	-0.9±1.8	50	-0.9±1.8	-1.1±1.9	47	-1.1±1.9	-0.7±1.8	48	-0.7±1.8	-1.2±1.9	49	-1.2±1.9
Mean urgency score ± SD (0–9)	-1.1±1.6	50	-1.1±1.6	-1±1.6	47	-1±1.6	-0.9±1.6	48	-0.9±1.6	-1.2±1.6	49	-1.2±1.6
Mean 24-hr frequency ± SD	-0.4±5.0	47	**-0.4±5.1**	-1.3±5.3	45	**-1.3±6.2**	-0.9±6.3	44	-0.9±6.3	-0.7±4.8	48	**-0.8±5.1**
Mean IC Symptom Index (0–20) ± SD	-1.9±3.2	50	-1.9±3.2	-2.4±3.9	47	**-2.4±3.8**	-1.7±3.5	48	-1.7±3.5	-2.6±3.4	49	-2.6±3.4
Mean IC Problem Index (0–16) ± SD	-2.1±3.2	50	**-2±3.2**	-2.4±3.2	47	-2.4±3.2	-1.9±2.8	48	-1.9±2.8	-2.6±3.5	49	-2.6±3.5
Mean Wisconsin IC Score (0–42) ± SD	-6.1±9.3	50	-6.1±9.3	-6.9±7.7	46	**-6.9±7.6**	-6.7±8.2	48	**-6.7±8.1**	-6.2±8.9	48	-6.2±8.9

*Not tabulated in DSIC. Published results for secondary end points include only those cases with complete data at baseline and 24 weeks, do not represent an intent to treat analysis and should be interpreted cautiously due to the potential bias in withdrawal from study

TABLE E. DSIC results from Sant et al (2003) Table 4. Changes in symptoms from baseline to 24 weeks by individual treatment arm.

	Placebo			Hydroxyzine Alone			PPS Alone			Combination		
	Published	DSIC N	DSIC:Mean SD or %	Published	DSIC N	DSIC:Mean SD or %	Published	DSIC N	DSIC:Mean SD or %	Published	DSIC N	DSIC: Mean SD or %
No. subjects randomized	31	31		31	31		29	29		30	30	
No. responders (%):	4(13)		4(13)	7(23)		7(23)	8(28)		8(28)	12(40)		12(40)
No.complete secondary endpoint data (%)*												
Mean pain score ± SD (0-9)	-1.0±1.8	24	-1.0±1.8	-0.5±1.8	24	-0.5±1.8	-0.8±1.8	26	-0.8±1.8	-1.6±1.9	23	-1.6±1.9
Mean urgency score ± SD (0–9)	-1.1±1.7	24	-1.1±1.7	-0.8±1.6	24	-0.8±1.6	-1.0±1.6	26	-1.0±1.6	-1.3±1.6	23	-1.3±1.6
Mean 24-hr frequency ± SD	-0.5±5.3	22	-0.5±5.3	-1.2±7.3	22	-1.2±7.3	-0.2±5.0	25	-0.2±5.0	-1.4±4.4	23	**-1.4±5.1**
Mean IC Symptom Index (0–20) ± SD	-2.3±3.4	24	-2.3±3.4	-1.3±3.6	24	-1.3±3.6	-1.7±3.0	26	-1.7±3.0	-3.6±4	23	**-3.6±3.6**
Mean IC Problem Index (0–16) ± SD	-2.3±3.1	24	-2.3±3.1	-1.5±2.6	24	-1.5±2.6	-1.9±3.3	26	-1.9±3.3	-3.4±3.6	23	-3.4±3.6
Mean Wisconsin IC Score (0–42) ± SD	-7.2±9.1	24	-7.2±9.1	-6.2±7.4	24	**-6.2±7.2**	-5±9.5	26	-5±9.5	-7.5±8.2	22	-7.5±8.2

*Not tabulated in DSIC. Published results for secondary end points include only those cases with complete data at baseline and 24 weeks, do not represent an intent to treat analysis and should be interpreted cautiously due to the potential bias in withdrawal from study

ATTACHMENT 1

Full Text of Article

ATTACHMENT 2

STATA Code for Tabulations from the ICCTG-PPS, Hydroxyzine Data in the NIDDK Repository

```
/*****icctgrct1.dta***/
/******Use Analysis data set*******/

/*******TABLE 2. Baseline characteristics by treatment group********/
tab1 arm treatment
tab arm treatment
tab gender
label define gender 0"female" 1"male"
label values gender gender
tab race
recode race (2=2) (3=3) (5=1) (1 4 6 7=4)
label define race 1"white" 2"black" 3"Hispanic" 4"other"
label values race race
summarize age
****create mean pain urgency and frequency scores
tab1 pain1 pain2 urgency1 urgency2 freq1 freq2 voidfreq_base wisc_base
gen pain_x=(pain1+pain2)/2
gen urgency_x=(urgency1+urgency2)/2
gen freq_x=(freq1+freq2)/2

**Create baseline IC symptom & problem index variables from 24 wk and change from 24 wk variables**
****no missing values n=97******
gen icsymp_base=icindexsym_24wk-icindexsym_chgbase24wk
gen icpro_base=icindexpro_24wk-icindexpro_chgbase24wk
tab1 icsymp_base icpro_base

tab treatment gender, row
tab treatment race, row
sort treatment
by treatment: summarize age pain_x urgency_x freq_x voidfreq_base icsymp_base icpro_base wisc_base


/******TABLE 3********/
/****Changes in symptoms from baseline to 24 weeks by main comparisons*****/
encode treatment, gen (PPS)
```

```
recode PPS (2 4=1) (1 3=2)
label define  dose 1"placebo" 2"drug"
label values PPS dose

encode treatment, gen (hydroxy)
recode hydroxy (3 4=1) (1 2=2)
label values hydroxy dose
tab1 PPS hydroxy

tab treatment PPS, row
tab PPS response, row
sort PPS
by PPS: summarize treatment globresp pain_chgbase24wk urgency_chgbase24wk voidfreq_chgbase24wk
icindexsym_chgbase24wk icindexpro_chgbase24wk wisc_chgbase24wk

tab treatment hydroxy, row
tab hydroxy response, row
sort hydroxy
by hydroxy: summarize treatment globresp pain_chgbase24wk urgency_chgbase24wk voidfreq_chgbase24wk
icindexsym_chgbase24wk icindexpro_chgbase24wk wisc_chgbase24wk


/***TABLE 4. Changes in symptoms from baseline to 24 weeks by treatment arm***/
tab treatment response, row
sort treatment
by treatment: summarize globresp pain_chgbase24wk urgency_chgbase24wk voidfreq_chgbase24wk
icindexsym_chgbase24wk icindexpro_chgbase24wk wisc_chgbase24wk
```